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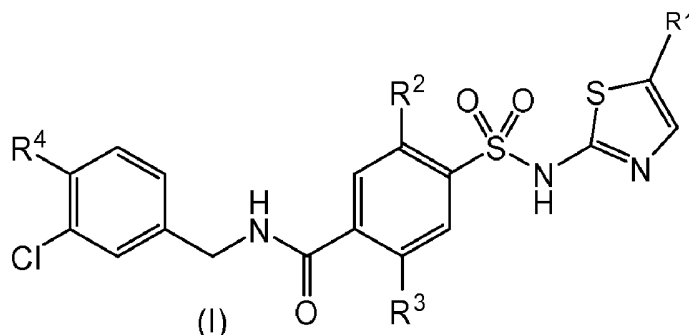
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(54) Title: BENZAMIDE DERIVATIVES



(57) **Abstract:** The present invention relates to compounds of the formula (I) and pharmaceutically acceptable salts and solvates thereof, to processes for the preparation of, intermediates used in the preparation of, and compositions containing such compounds and the uses of such compounds in the treatment of pain.

BENZAMIDE DERIVATIVES

This invention relates to benzamide derivatives. More particularly, this invention relates to thiazolylaminosulfonylbenzamide derivatives and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

The benzamide derivatives of the present invention are sodium channel modulators and have a number of therapeutic applications, particularly in the treatment of pain.

Voltage-gated sodium channels are found in all excitable cells including myocytes of muscle and neurons of the central and peripheral nervous system. In neuronal cells, sodium channels are primarily responsible for generating the rapid upstroke of the action potential. In this manner sodium channels are essential to the initiation and propagation of electrical signals in the nervous system. Proper and appropriate function of sodium channels is therefore necessary for normal function of the neuron. Consequently, aberrant sodium channel function is thought to underlie a variety of medical disorders (see Hubner CA, Jentsch TJ, *Hum. Mol. Genet.*, **11(20)**: 2435-45 (2002) for a general review of inherited ion channel disorders) including epilepsy (Yogeeswari *et al.*, *Curr. Drug Targets*, **5(7)**: 589-602 (2004)), arrhythmia (Noble D., *Proc. Natl. Acad. Sci. USA*, **99(9)**: 5755-6 (2002)) myotonia (Cannon, SC, *Kidney Int.* **57(3)**: 772-9 (2000)), and pain (Wood, JN *et al.*, *J. Neurobiol.*, **61(1)**: 55-71 (2004)). See Table A, below.

Table A

Type	Gene Symbol	Primary tissue	TTX IC-50	Disease association	Indications	
Na _v 1.1	SCN1A	CNS/PNS	10	Epilepsy	Pain,	seizures,

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Type	Gene Symbol	Primary tissue	TTX IC-50	Disease association	Indications
Na _v 1.2	SCN2A	CNS	10	Epilepsy	neurodegeneration Epilepsy, neurodegeneration
Na _v 1.3	SCN3A	CNS	15	---	Pain
Na _v 1.4	SCN4A	Sk. muscle	25	Myotonia	Myotonia
Na _v 1.5	SCN5A	Heart	2000	Arrhythmia	Arrhythmia
Na _v 1.6	SCN8A	CNS/PNS	6	---	Pain, movement disorders
Na _v 1.7	SCN9A	PNS	25	Erythralgia	Pain
Na _v 1.8	SCN10A	PNS	50000	---	Pain
Na _v 1.9	SCN11A	PNS	1000	---	Pain

There are currently at least nine known members of the family of voltage-gated sodium channel (VGSC) alpha subunits. Names for this family include SCN_x, SCN_{Ax}, and Na_v_{x.x}. The VGSC family has been phylogenetically divided into two subfamilies Na_v1._x (all but SCN6A) and Na_v2._x (SCN6A). The Nav1._x subfamily can be functionally subdivided into two groups, those which are sensitive to blocking by tetrodotoxin (TTX-sensitive or TTX-s) and those which are resistant to blocking by tetrodotoxin (TTX-resistant or TTX-r).

There are three members of the subgroup of TTX-resistant sodium channels. The SCN5A gene product (Na_v1.5, H1) is almost exclusively expressed in cardiac tissue and has been shown to underlie a variety of cardiac arrhythmias and conduction disorders (Liu H, *et al.*, *Am. J. Pharmacogenomics*, **3(3)**: 173-9 (2003)). Consequently, blockers of Nav1.5 have found clinical utility in treatment of such disorders (Srivatsa U, *et al.*, *Curr. Cardiol. Rep.*, **4(5)**: 401-10 (2002)). The remaining TTX-resistant sodium channels, Nav1.8 (SCN10A, PN3, SNS) and Nav1.9 (SCN11A, NaN, SNS2) are expressed in the peripheral nervous

system and show preferential expression in primary nociceptive neurons. Human genetic variants of these channels have not been associated with any inherited clinical disorder. However, aberrant expression of Nav1.8 has been found in the CNS of human multiple sclerosis (MS) patients and also in a rodent model of MS (Black, JA, *et al.*, *Proc. Natl. Acad. Sci. USA*, **97**(21): 11598-602 (2000)). Evidence for involvement in nociception is both associative (preferential expression in nociceptive neurons) and direct (genetic knockout). Nav1.8-null mice exhibited typical nociceptive behavior in response to acute noxious stimulation but had significant deficits in referred pain and hyperalgesia (Laird JM, *et al.*, *J. Neurosci.*, **22**(19):8352-6 (2002)).

The TTX-sensitive subset of voltage-gated sodium channels is expressed in a broader range of tissues than the TTX-resistant channels and has been associated with a variety of human disorders. The Nav1.1 channel well exemplifies this general pattern, as it is expressed in both the central and peripheral nervous system and has been associated with several seizure disorders including Generalized Epilepsy with Febrile Seizures Plus, types 1 and 2 (GEFS+1, GEFS+2), Severe Myoclonic Epilepsy of Infancy (SMEI), and others (Claes, L, *et al.*, *Am. J. Hum. Genet.*, **68**: 1327-1332 (2001); Escayg, A., *Am. J. Hum. Genet.*, **68**: 866-873 (2001); Lossin, C, *Neuron*, **34**: 877-884 (2002)). The Nav1.2 channel is largely, if not exclusively, expressed in the central nervous system and quantitative studies indicate it is the most abundant VGSC of the CNS. Mutations of Nav1.2 are also associated with seizure disorders (Berkovic, S. F., *et al.*, *Ann. Neurol.*, **55**: 550-557 (2004)) and Nav1.2-null "knockout" mice exhibit perinatal lethality (Planells-Cases R *et al.*, *Biophys. J.*, **78**(6):2878-91 (2000)). Expression of the Nav1.4 gene is largely restricted to skeletal muscle and, accordingly, mutations of this gene are associated with a variety of movement disorders (Ptacek, L. J., *Am. J. Hum. Genet.*, **49**: 851-854 (1991); Hudson AJ, *Brain*, **118**(2): 547-63 (1995)). The majority of these disorders are related to hyperactivity or "gain-of-function" and have been found to respond to

treatment with sodium channel blockers (Desaphy JF, *et al.*, *J. Physiol.*, **554(2)**: 321-34 (2004)).

Neither the SCN3A nor the SCN8A VGSC genes have been conclusively linked to heritable disorders in humans. Loss-of-function mutations of the SCN8A gene are known in mice and yield increasingly debilitating phenotypes, dependent upon the remaining functionality of the gene products (Meisler MH, *Genetica*, **122(1)**: 37-45 (2004)). Homozygous null mutations cause progressive motor neuron failure leading to paralysis and death, while heterozygous null animals are asymptomatic. Homozygous *med^J* mice have nearly 90% reduction in functional Nav1.6 current and exhibit dystonia and muscle weakness but are still viable. Evidence for Nav1.6 being important for nociception is largely associative as Nav1.6 is expressed at high levels in dorsal root ganglia and can be found in spinal sensory tracts (Tzoumaka E, *J. Neurosci. Res.*, **60(1)**: 37-44 (2000)). It should be noted however that expression of Nav1.6 is not restricted to sensory neurons of the periphery. Like the Nav1.6 channel, expression of the Nav1.3 VGSC can also be detected in both the central and peripheral nervous system, though levels in the adult CNS are generally much higher than PNS. During development and the early postnatal period, Nav1.3 is expressed in peripheral neurons but this expression wanes as the animal matures (Shah BS, *J. Physiol.*, **534(3)**: 763-76 (2001); Schaller KL, *Cerebellum*, **2(1)**: 2-9 (2003)). Following neuronal insult, Nav1.3 expression is upregulated, more closely mimicking the developmental expression patterns (Hains BC, *J. Neurosci.*, **23(26)**: 8881-92 (2003)). Coincident with the recurrence of Nav1.3 expression is the emergence of a rapidly re-priming sodium current in the injured axons with a biophysical profile similar to Nav1.3 (Leffler A, *et al.*, *J. Neurophysiol.*, **88(2)**: 650-8 (2002)). Treatment of injured axons with high levels of GDNF has been shown to diminish the rapidly repriming sodium current and reverse thermal and mechanical pain-related behaviors in a rat model of nerve injury, presumably by down-regulating the expression of Nav1.3 (Boucher TJ, *Curr. Opin. Pharmacol.*, **1(1)**: 66-72

(2001)). Specific down-regulation of Nav1.3 via treatment with antisense oligonucleotides has also been shown to reverse pain-related behaviors following spinal cord injury (Hains BC, *J. Neurosci.*, **23(26)**: 8881-92 (2003)).

Sodium channel-blocking agents have been reported to be effective in the treatment of various disease states, and have found particular use as local anesthetics and in the treatment of cardiac arrhythmias. It has also been reported that sodium channel-blocking agents may be useful in the treatment of pain, including acute, chronic, inflammatory and/or neuropathic pain; see, for example, Wood, JN *et al.*, *J. Neurobiol.*, **61(1)**: 55-71 (2004). Preclinical evidence demonstrates that sodium channel-blocking agents can suppress neuronal firing in peripheral and central sensory neurons, and, it is via this mechanism, that they may be useful for relieving pain. In some instances, abnormal or ectopic firing can originate from injured or otherwise sensitized neurons. For example, it has been shown that sodium channels can accumulate in peripheral nerves at sites of axonal injury and may function as generators of ectopic firing (Devor *et al. J. Neurosci.*, **132**: 1976 (1993)). Changes in sodium channel expression and excitability have also been shown in animal models of inflammatory pain where treatment with proinflammatory materials (CFA, Carrageenan) promoted pain-related behaviors and correlated with increased expression of sodium channel subunits (Gould *et al.*, *Brain Res.*, **824(2)**: 296-9 (1999); Black *et al.*, *Pain*, **108(3)**: 237-47 (2004)). Alterations in either the level of, expression of, or distribution of sodium channels, therefore, may have a major influence on neuronal excitability and pain-related behaviors. As such there is a desire to seek new sodium channel modulators.

International patent application WO 2005 / 013914 (publication date 17th February 2005) discloses compounds, in particular heteroaryl amino sulfonylphenyl derivatives, which are useful as inhibitors of voltage gated sodium channels with a number of therapeutic uses, including the treatment of pain.

International patent application WO 2008 / 118758 (publication date 2nd October 2008) discloses compounds, in particular aryl sulphonamides, which are sodium channel modulators with a number of therapeutic uses, particularly for the treatment of pain.

However, there remains a need for still further new sodium channel modulators. The compounds of the present invention described herein are preferential Nav1.3 channel modulators. In particular, they show an affinity for the Nav1.3 channel which is greater than their affinity for the Nav1.5 channel. Preferred compounds of the present invention show at least a 20-fold selectivity for the Nav1.3 channel as compared with the Nav1.5. In addition, preferred compounds of the present invention have improved pharmacokinetic properties.

The compounds of the present invention, being Nav1.3 modulators, are therefore potentially useful in the treatment of a wide range of disorders, particularly pain. The treatment of pain is a preferred use. All forms of pain are potentially treatable with the compounds of the present invention including acute pain; chronic pain; neuropathic pain; inflammatory pain; visceral pain; nociceptive pain including post-surgical pain; and mixed pain types involving the viscera, gastrointestinal tract, cranial structures, musculoskeletal system, spine, urogenital system, cardiovascular system and CNS, including cancer pain, back and orofacial pain.

Other conditions that may be treated with the compounds of the present invention include anal fissure, neuronal injury, spinal injury and epilepsy.

It is an objective of the invention to provide new Nav1.3 channel modulators and, that preferably, such new modulators are suitable for further development as drug candidates. In general, such preferred compounds should bind potently to

the Nav1.3 channel, show functional activity as Nav1.3 channel modulators and preferably show little affinity for other sodium channels, particularly Nav1.5. Furthermore, the preferred compounds should have one or more of the following improved properties: be well absorbed from the gastrointestinal tract; have an improved metabolic profile, in particular with respect to the toxicity or allergenicity of any metabolites formed; or possess more favourable pharmacokinetic properties. It is further preferred that they should also be non-toxic and demonstrate few side-effects. Furthermore, such preferred drug candidates should preferably exist in a physical form that is stable, non-hygroscopic and easily formulated. Preferred benzamide derivatives of the present invention are selective for the Nav1.3 channel over Nav1.5, which may potentially lead to one or more improvements in the side-effect profile.

Summary of the invention

The invention therefore provides, as Embodiment 1, a compound selected from the following group:

N-[3-chloro-4-(trifluoromethoxy)benzyl]-3-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide;

N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide;

N-[3-chloro-4-(trifluoromethoxy)benzyl]-2-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide;

N-[3-chloro-4-(trifluoromethyl)benzyl]-2-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide;

N-[3-chloro-4-(trifluoromethoxy)benzyl]-2-fluoro-4-[(5-fluoro-1,3-thiazol-2-yl)amino]sulfonyl}benzamide;

N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(5-fluoro-1,3-thiazol-2-yl)amino]sulfonyl}benzamide;

N-[3-chloro-4-(trifluoromethyl)benzyl]-4-[(5-fluoro-1,3-thiazol-2-yl)amino]sulfonyl}benzamide; and

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N-[3-chloro-4-(trifluoromethoxy)benzyl]-3-fluoro-4-[(5-fluoro-1,3-thiazol-2-yl)amino]sulfonylbenzamide;

or a pharmaceutically acceptable salt, solvate or tautomer thereof.

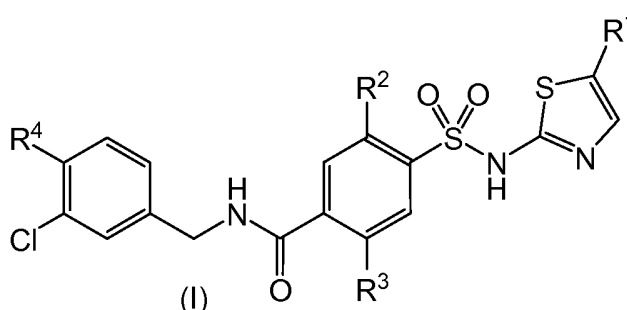
In a preferred embodiment, Embodiment 2, the invention provides a compound selected from the following group:

N-[3-chloro-4-(trifluoromethoxy)benzyl]-3-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide

N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide

and the pharmaceutically acceptable salts, solvates and tautomers thereof.

In another aspect, this invention provides, as Embodiment 3, a compound of formula (I):



or a pharmaceutically acceptable salt, solvate or tautomer thereof,

wherein R¹ is hydrogen or fluoro;

R² is fluoro and R³ is hydrogen; or R² is hydrogen and R³ is fluoro; or R² and R³ are both hydrogen; and

R⁴ is trifluoromethyl or trifluoromethoxy;

with the proviso that the compound of formula (I) is not N-[3-chloro-4-(trifluoromethyl)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide; and

with the further proviso that the compound of formula (I) is not N-[3-chloro-4-(trifluoromethyl)benzyl]-3-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide.

In a preferred aspect, Embodiment 4, the invention provides a compound of formula (I), or a pharmaceutically acceptable salt, solvate or tautomer thereof, according to Embodiment 3, wherein R^4 is trifluoromethoxy.

In another embodiment, Embodiment 5, the invention provides for a compound selected from the following group:

N-[3-chloro-4-(trifluoromethyl)benzyl]-3-fluoro-4-[(5-fluoro-1,3-thiazol-2-yl)amino]sulfonyl}benzamide;

N-[3-chloro-4-(trifluoromethyl)benzyl]-2-fluoro-4-[(5-fluoro-1,3-thiazol-2-yl)amino]sulfonyl}benzamide;

or a pharmaceutically acceptable salt, solvate or tautomer thereof.

In yet another embodiment, Embodiment 6, the invention provides for a prodrug of compounds of Embodiment 1, Embodiment 2, Embodiment 3, Embodiment 4, or Embodiment 5 wherein the hydrogen of the –NH-group of the sulphonamide moiety or the hydrogen of the –NH-group of the 1, 3-thiazolyl ring of such compounds is replaced by either –CH₂OP(=O)(OR')₂ or –CH₂OC(=O)R' wherein R' is selected from the group consisting of hydrogen or (C₁-C₆)alkyl, for example -C(CH₃)₃, or a pharmaceutically acceptable salt, solvate or tautomer thereof.

In a preferred embodiment, Embodiment 7, the invention provides for a prodrug of compounds of Embodiment 1, Embodiment 2, Embodiment 3, Embodiment 4, or Embodiment 5 wherein the hydrogen of the –NH-group of the sulphonamide moiety or the hydrogen of the –NH-group of the 1, 3-thiazolyl ring of such compounds is replaced by –CH₂OP(=O)(OR')₂, in particular wherein R' is hydrogen to give -CH₂OP(=O)(OH)₂, or where R' is -C(CH₃)₃ to give -CH₂OP(=O)(OC(CH₃)₃)₂, or a pharmaceutically acceptable salt, solvate or tautomer thereof.

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In a preferred embodiment, Embodiment 8, the invention provides for a prodrug selected from the following group:

[(2Z)-2-{{(4-{{(3-chloro-4-(trifluoromethoxy)benzyl]carbamoyl}phenyl)sulfonyl]imino}-1,3-thiazol-3(2H)-yl)methyl dihydrogen phosphate; and
 di-*tert*-butyl [(2Z)-2-{{(4-{{(3-chloro-4-(trifluoromethoxy)benzyl]carbamoyl}phenyl)sulfonyl]imino}-1,3-thiazol-3(2H)-yl)methyl phosphate

or a pharmaceutically acceptable salt, solvate or tautomer thereof.

Brief Description of the Drawings

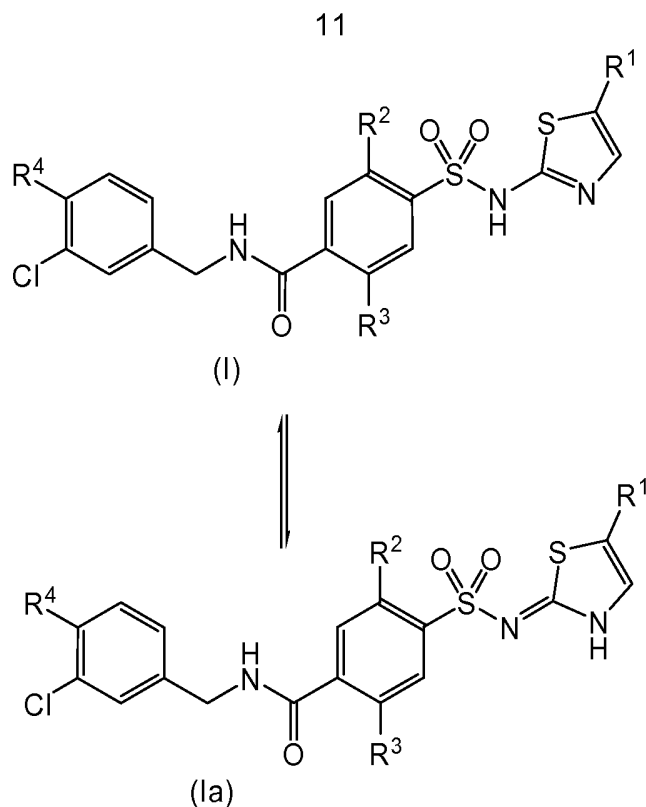
Figure 1 shows log linear in vivo pK data obtained with compounds of the invention.

Figure 2 shows log log in vivo pK data obtained with compounds of the invention.

Detailed Description

As used herein the term compounds of the invention means, unless otherwise stated, compounds of Embodiment 1, Embodiment 2, Embodiment 3, Embodiment 4, Embodiment 5, Embodiment 6, Embodiment 7 and Embodiment 8. In each case, where relevant, compounds N-[3-chloro-4-(trifluoromethyl)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide; and N-[3-chloro-4-(trifluoromethyl)benzyl]-3-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide are disclaimed.

Compounds of Embodiment 1, Embodiment 2, Embodiment 3, Embodiment 4, or Embodiment 5, may generally be schematically represented by a formula (I), wherein R¹, R², R³ and R⁴ are as defined above for Embodiment 3. Such compounds may tautomerise to provide a compound of the formula (Ia):



All references to compounds of the invention that encompass compounds of Embodiment 1, Embodiment 2, Embodiment 3, Embodiment 4, or Embodiment 5, or to compounds of formula (I), include the tautomeric isomers of the general schematic form shown in formula (Ia).

As used herein the term alkyl means an alicyclic, saturated hydrocarbon chain of the formula C_nH_{2n+1} which may be linear or branched. Examples of such groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl and hexyl.

As used herein the term aryl means a phenyl ring or a 5- or 6-membered aromatic heterocyclic group both of which can be optionally substituted with one or more substituents selected from the group consisting of halo, CN, halo(C_1 - C_4)alkyl, halo(C_1 - C_4)alkoxy, and NO_2 .

As used herein the term halo means fluoro, chloro, bromo or iodo.

As used herein the term alkoxy means an alicyclic, saturated hydrocarbon chain of the formula $\text{OC}_n\text{H}_{2n+1}$ which may be linear or branched. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy.

As used herein the terms haloalkyl and haloalkoxy mean an alkyl or alkoxy group, containing the requisite number of carbon atoms, substituted with one or more halo atoms.

Pharmaceutically acceptable salts of the compounds of the invention include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzone, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

A pharmaceutically acceptable salt of a compound of the invention may be readily prepared by mixing together solutions of the compound of the invention and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Halebian (August 1975).

Included within the scope of the present invention are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Hereinafter all references to compounds of the invention include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

The compounds of the invention include compounds of the invention as hereinbefore defined, including salts, solvates and complexes thereof, and polymorphs, prodrugs, and tautomers thereof as hereinafter defined and isotopically-labeled compounds of the invention.

As stated, the invention includes all polymorphs of the compounds of the invention as hereinbefore defined.

Also within the scope of the invention are so-called 'prodrugs' of the compounds of invention. Thus certain derivatives of compounds of the invention, in particular of Embodiment 1, Embodiment 2, Embodiment 3, Embodiment 4 or Embodiment 5, which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of the invention having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of invention with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

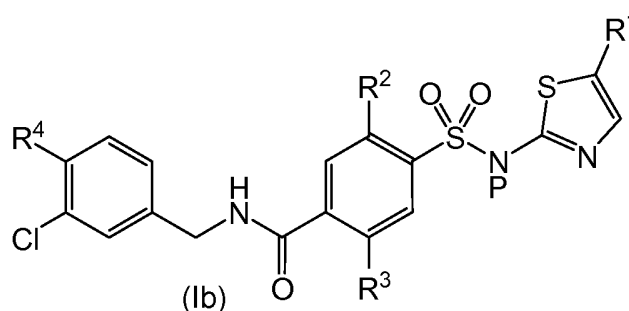
Some examples of prodrugs in accordance with the invention include where the compound of the invention contains a sulfonamide functionality (-SO₂-NHR-

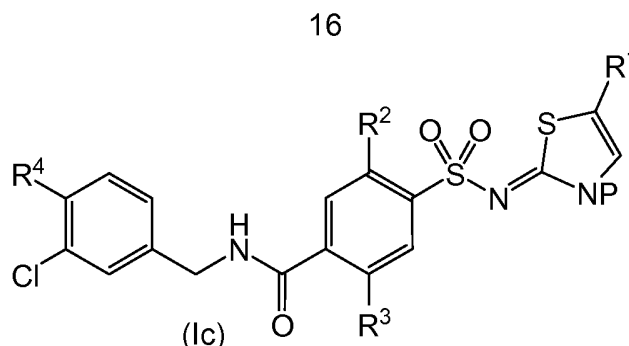
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where $R \neq H$), an amide thereof, for example, replacement of the hydrogen atom with (C_1-C_{10}) alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

A particularly useful prodrug of compounds of Embodiment 1, Embodiment 2, Embodiment 3, Embodiment 4 or Embodiment 5 is formed by replacement of the hydrogen of the $-NH$ -group of the sulphonamide moiety or the hydrogen of the $-NH$ -group of the 1, 3-thiazolyl ring of such compounds is replaced by either $-CH_2OP(=O)(OR')_2$ or $-CH_2OC(=O)R'$ wherein R' is selected from the group consisting of hydrogen or (C_1-C_6) alkyl, for example $-C(CH_3)_3$. Such compounds are prepared by reaction of the $-NH$ -group of the sulphonamide moiety or the $-NH$ -group of the 1, 3-thiazolyl ring of the compounds of Embodiment 1, Embodiment 2, Embodiment 3, Embodiment 4 or Embodiment 5 with either an alkyl linked phosphate, such as an alkyl linked phosphoric acid or an alkyl linked phosphate ester, or with an alkyl linked carboxylic acid group, such as an alkyl linked carboxylic acid or an alkyl linked carboxylic ester. Such prodrug compounds can generally be schematically represented as shown below by formula (Ib) or (Ic):





wherein R^1 , R^2 , R^3 and R^4 are as defined in Embodiment 3 and wherein P is the prodrug moiety as defined above. Phosphate prodrugs have been generally described in, for example, Rautio, J.; Kumpulainen, H.; Heimbach, T.; Oliyai, R.; Oh, D.; Järvinen, T.; Savolainen, J. *Nat. Rev. Drug Discovery* **2008**, 7, 255. Carboxylic acid and related ester prodrugs have been generally described in Calheiros, T.; Iley, J.; Lopes, F.; Moreira, R. *Bioorg. Med. Chem. Lett.* **1995**, 5, 937 and in Lopes, F.; Moreira, R.; Iley, J. *Bioorg. Med. Chem.* **2000**, 8, 707.

When forming such prodrugs it is preferred that the hydrogen of the –NH-group of the sulphonamide moiety or the hydrogen of the –NH-group of the 1, 3-thiazolyl ring of such compounds is replaced by –CH₂OP(=O)(OR')₂, in particular wherein R' is hydrogen to give –CH₂OP(=O)(OH)₂, or where R' is –C(CH₃)₃ to give –CH₂OP(=O)(OC(CH₃)₃)₂. Particularly preferred prodrugs of the present invention are [(2Z)-2-{[(4-{[3-chloro-4-(trifluoromethoxy)benzyl]carbamoyl}phenyl)sulfonyl]imino}-1,3-thiazol-3(2H)-yl]methyl dihydrogen phosphate and di-*tert*-butyl [(2Z)-2-{[(4-{[3-chloro-4-(trifluoromethoxy)benzyl]carbamoyl}phenyl)sulfonyl]imino}-1,3-thiazol-3(2H)-yl]methyl phosphate.

As such the invention specifically provides for such preferred prodrugs as set out in Embodiment 6, Embodiment 7 or Embodiment 8 above, and their pharmaceutically acceptable salts, solvates or tautomers thereof. Such prodrugs are particularly useful because of their potential for improved bioavailability when

compared to the parent compound, ie that with the unsubstituted amino group moiety.

Finally, certain compounds of the invention may themselves act as prodrugs of other compounds of the invention.

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , and sulphur, such as ^{35}S .

Certain isotopically-labelled compounds of the invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^3H , and carbon-14, *i.e.* ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D₂O, d₆-acetone, d₆-DMSO.

The compounds of the invention, being Nav1.3 channel modulators, or pro-drugs of such modulators, are potentially useful in the treatment of a range of disorders. The treatment of pain is a preferred use.

Physiological pain is an important protective mechanism designed to warn of danger from potentially injurious stimuli from the external environment. The system operates through a specific set of primary sensory neurones and is activated by noxious stimuli *via* peripheral transducing mechanisms (see Millan, 1999, Prog. Neurobiol., 57, 1-164 for a review). These sensory fibres are known as nociceptors and are characteristically small diameter axons with slow conduction velocities. Nociceptors encode the intensity, duration and quality of noxious stimulus and by virtue of their topographically organised projection to the spinal cord, the location of the stimulus. The nociceptors are found on nociceptive nerve fibres of which there are two main types, A-delta fibres (myelinated) and C fibres (non-myelinated). The activity generated by nociceptor input is transferred, after complex processing in the dorsal horn, either directly, or via brain stem relay nuclei, to the ventrobasal thalamus and then on to the cortex, where the sensation of pain is generated.

Pain may generally be classified as acute or chronic. Acute pain begins suddenly and is short-lived (usually twelve weeks or less). It is usually associated with a specific cause such as a specific injury and is often sharp and severe. It is the kind of pain that can occur after specific injuries resulting from surgery, dental work, a strain or a sprain. Acute pain does not generally result in any persistent psychological response. In contrast, chronic pain is long-term pain, typically persisting for more than three months and leading to significant psychological and emotional problems. Common examples of chronic pain are neuropathic pain (e.g. painful diabetic neuropathy, postherpetic neuralgia), carpal tunnel syndrome, back pain, headache, cancer pain, arthritic pain and chronic post-surgical pain.

When a substantial injury occurs to body tissue, *via* disease or trauma, the characteristics of nociceptor activation are altered and there is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. These effects lead to a heightened sensation of pain. In acute pain these mechanisms can be useful, in promoting protective behaviours which may better enable repair processes to take place. The normal expectation would be that sensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is often due to nervous system injury. This injury often leads to abnormalities in sensory nerve fibres associated with maladaptation and aberrant activity (Woolf & Salter, 2000, *Science*, 288, 1765-1768).

Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. Patients tend to be quite heterogeneous and may present with various pain symptoms. Such symptoms include: 1) spontaneous pain which may be dull, burning, or stabbing; 2) exaggerated pain responses to noxious stimuli (hyperalgesia); and 3) pain produced by normally innocuous stimuli (allodynia - Meyer et al., 1994, *Textbook of Pain*, 13-44). Although

patients suffering from various forms of acute and chronic pain may have similar symptoms, the underlying mechanisms may be different and may, therefore, require different treatment strategies. Pain can also therefore be divided into a number of different subtypes according to differing pathophysiology, including nociceptive, inflammatory and neuropathic pain.

Nociceptive pain is induced by tissue injury or by intense stimuli with the potential to cause injury. Pain afferents are activated by transduction of stimuli by nociceptors at the site of injury and activate neurons in the spinal cord at the level of their termination. This is then relayed up the spinal tracts to the brain where pain is perceived (Meyer et al., 1994, Textbook of Pain, 13-44). The activation of nociceptors activates two types of afferent nerve fibres. Myelinated A-delta fibres transmit rapidly and are responsible for sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey a dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of pain from central nervous system trauma, strains/sprains, burns, myocardial infarction and acute pancreatitis, post-operative pain (pain following any type of surgical procedure), posttraumatic pain, renal colic, cancer pain and back pain. Cancer pain may be chronic pain such as tumour related pain (e.g. bone pain, headache, facial pain or visceral pain) or pain associated with cancer therapy (e.g. postchemotherapy syndrome, chronic postsurgical pain syndrome or post radiation syndrome). Cancer pain may also occur in response to chemotherapy, immunotherapy, hormonal therapy or radiotherapy. Back pain may be due to herniated or ruptured intervertebral discs or abnormalities of the lumbar facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament. Back pain may resolve naturally but in some patients, where it lasts over 12 weeks, it becomes a chronic condition which can be particularly debilitating.

Neuropathic pain is currently defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system. Nerve damage can be caused by trauma and disease and thus the term 'neuropathic pain' encompasses many disorders with diverse aetiologies. These include, but are not limited to, peripheral neuropathy, diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, back pain, cancer neuropathy, HIV neuropathy, phantom limb pain, carpal tunnel syndrome, central post-stroke pain and pain associated with chronic alcoholism, hypothyroidism, uremia, multiple sclerosis, spinal cord injury, Parkinson's disease, epilepsy and vitamin deficiency. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patient's quality of life (Woolf and Mannion, 1999, *Lancet*, 353, 1959-1964). The symptoms of neuropathic pain are difficult to treat, as they are often heterogeneous even between patients with the same disease (Woolf & Decosterd, 1999, *Pain Supp.*, 6, S141-S147; Woolf and Mannion, 1999, *Lancet*, 353, 1959-1964). They include spontaneous pain, which can be continuous, and paroxysmal or abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

The inflammatory process is a complex series of biochemical and cellular events, activated in response to tissue injury or the presence of foreign substances, which results in swelling and pain (Levine and Taiwo, 1994, *Textbook of Pain*, 45-56). Arthritic pain is the most common inflammatory pain. Rheumatoid disease is one of the commonest chronic inflammatory conditions in developed countries and rheumatoid arthritis is a common cause of disability. The exact aetiology of rheumatoid arthritis is unknown, but current hypotheses suggest that both genetic and microbiological factors may be important (Grennan & Jayson, 1994, *Textbook of Pain*, 397-407). It has been estimated that almost 16 million Americans have symptomatic osteoarthritis (OA) or degenerative joint disease,

most of whom are over 60 years of age, and this is expected to increase to 40 million as the age of the population increases, making this a public health problem of enormous magnitude (Houge & Mersfelder, 2002, *Ann Pharmacother.*, 36, 679-686; McCarthy et al., 1994, *Textbook of Pain*, 387-395). Most patients with osteoarthritis seek medical attention because of the associated pain. Arthritis has a significant impact on psychosocial and physical function and is known to be the leading cause of disability in later life. Ankylosing spondylitis is also a rheumatic disease that causes arthritis of the spine and sacroiliac joints. It varies from intermittent episodes of back pain that occur throughout life to a severe chronic disease that attacks the spine, peripheral joints and other body organs.

Another type of inflammatory pain is visceral pain which includes pain associated with inflammatory bowel disease (IBD). Visceral pain is pain associated with the viscera, which encompass the organs of the abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain associated with the viscera can be divided into digestive visceral pain and non-digestive visceral pain. Commonly encountered gastrointestinal (GI) disorders that cause pain include functional bowel disorder (FBD) and inflammatory bowel disease (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including, in respect of FBD, gastro-esophageal reflux, dyspepsia, irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and, in respect of IBD, Crohn's disease, ileitis and ulcerative colitis, all of which regularly produce visceral pain. Other types of visceral pain include the pain associated with dysmenorrhea, cystitis and pancreatitis and pelvic pain.

It should be noted that some types of pain have multiple aetiologies and thus can be classified in more than one area, e.g. back pain and cancer pain have both nociceptive and neuropathic components.

Other types of pain include:

- pain resulting from musculo-skeletal disorders, including myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, glycogenolysis, polymyositis and pyomyositis;
- heart and vascular pain, including pain caused by angina, myocardical infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleredoma and skeletal muscle ischemia;
- head pain, such as migraine (including migraine with aura and migraine without aura), cluster headache, tension-type headache mixed headache and headache associated with vascular disorders; and
- orofacial pain, including dental pain, otic pain, burning mouth syndrome and temporomandibular myofascial pain.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).

ORAL ADMINISTRATION

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

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For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 wt% to 5 wt% of the tablet, and glidants may comprise from 0.2 wt% to 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

PARENTERAL ADMINISTRATION

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral

administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of the invention used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

TOPICAL ADMINISTRATION

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

INHALED/INTRANASAL ADMINISTRATION

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *L*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-co-glycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing the compound of the invention. The overall daily dose may be administered in a single dose or, more usually, as divided doses throughout the day.

RECTAL/INTRA VAGINAL ADMINISTRATION

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

OCULAR/AURAL ADMINISTRATION

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as cross-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelatin, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

OTHER TECHNOLOGIES

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and

gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

KIT-OF-PARTS

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula the invention in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

DOSAGE

For administration to human patients, the total daily dose of the compounds of the invention will depend on the mode of administration. For example, oral

administration may require a higher total daily dose than an intravenous dose. The total daily dose may be administered in single or divided doses.

For the avoidance of doubt, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

A Nav1.3 channel modulator may be usefully combined with another pharmacologically active compound, or with two or more other pharmacologically active compounds, particularly in the treatment of pain. For example, a Nav1.3 channel modulator, particularly a compound of the invention, or a pharmaceutically acceptable salt, solvate or tautomer thereof, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents selected from:

- an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;
- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;
- a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, theamylal or thiopental;
- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;

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- an H₁ antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphenadine;
- an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-methoxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®, a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (–)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(1H)-quinolinone};
- an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;
- an anticonvulsant, e.g. carbamazepine, lamotrigine, topiramate or valproate;
- a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6,13-dione (TAK-637), 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);

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- a muscarinic antagonist, e.g oxybutynin, tolterodine, propiverine, trospium chloride, darifenacin, solifenacin, temiverine and ipratropium;
- a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;
- a coal-tar analgesic, in particular paracetamol;
- a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonopiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclizine, Miraxion® or sarizotan;
- a vanilloid receptor agonist (e.g. resiniferatoxin) or antagonist (e.g. capsazepine);
- a beta-adrenergic such as propranolol;
- a local anaesthetic such as mexiletine;
- a corticosteroid such as dexamethasone;
- a 5-HT receptor agonist or antagonist, particularly a 5-HT_{1B/1D} agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;
- a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);
- a cholinergic (nicotinic) analgesic, such as ispronicline (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidylmethoxy)-2-chloropyridine (ABT-594) or nicotine;
- Tramadol®;
- a PDEV inhibitor, such as 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-1-

yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (varidenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidiny)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidiny)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;

- an alpha-2-delta ligand such as gabapentin, pregabalin, 3-methylgabapentin, (1 α ,3 α ,5 α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid;
- a cannabinoid;
- metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;
- a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine,

cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone;

- a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupropion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;
- a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and imipramine;
- an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)-butyl]thio]-5-chloro-3-pyridinecarbonitrile; 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3 pyridinecarbonitrile, 2-[[[(1R,3S)-3- amino-4-hydroxy- 1 -(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine, or guanidinoethyldisulfide;
- an acetylcholinesterase inhibitor such as donepezil;
- a prostaglandin E₂ subtype 4 (EP4) antagonist such as N-[(2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl)amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[(1S)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;

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- a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870,
- a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl),1,4-benzoquinone (CV-6504);
- a sodium channel blocker, such as lidocaine;
- a 5-HT3 antagonist, such as ondansetron;

and the pharmaceutically acceptable salts and solvates thereof.

Such combinations offer significant advantages, including synergistic activity, in therapy.

Inasmuch as it may be desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of the invention in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

It will be appreciated that within the scope of the present invention are provided the following:

- (i) a compound of the invention or a pharmaceutically acceptable salt, solvate or tautomer thereof;
- (ii) a process for the preparation of a compound of the invention or a pharmaceutically acceptable salt, solvate or tautomer thereof;
- (iii) a pharmaceutical composition including a compound of the invention or a pharmaceutically acceptable salt, solvate or tautomer thereof, together with a pharmaceutically acceptable excipient;
- (iv) a pharmaceutical composition including a compound of the invention or a pharmaceutically acceptable salt, solvate or tautomer thereof, together with a pharmaceutically acceptable excipient, for use in the treatment of a disease or condition for which a Nav1.3 channel modulator is indicated, particularly for the treatment of pain;
- (v) a compound of the invention or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;
- (vi) the use of a compound of the invention or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament to treat a disease or condition for which a Nav1.3 channel modulator is indicated, particularly for the treatment of pain;
- (vii) a compound of the invention or of a pharmaceutically acceptable salt, solvate or composition thereof, for use in the treatment of a disease or

condition for which a Nav1.3 channel modulator is indicated, particularly for use in the treatment of pain;

- (viii) a method of treating a disease or condition for which a Nav1.3 channel modulator is indicated in a mammal, including a human being, including administering to said mammal an effective amount of a compound of the invention or a pharmaceutically acceptable salt, solvate or composition thereof.

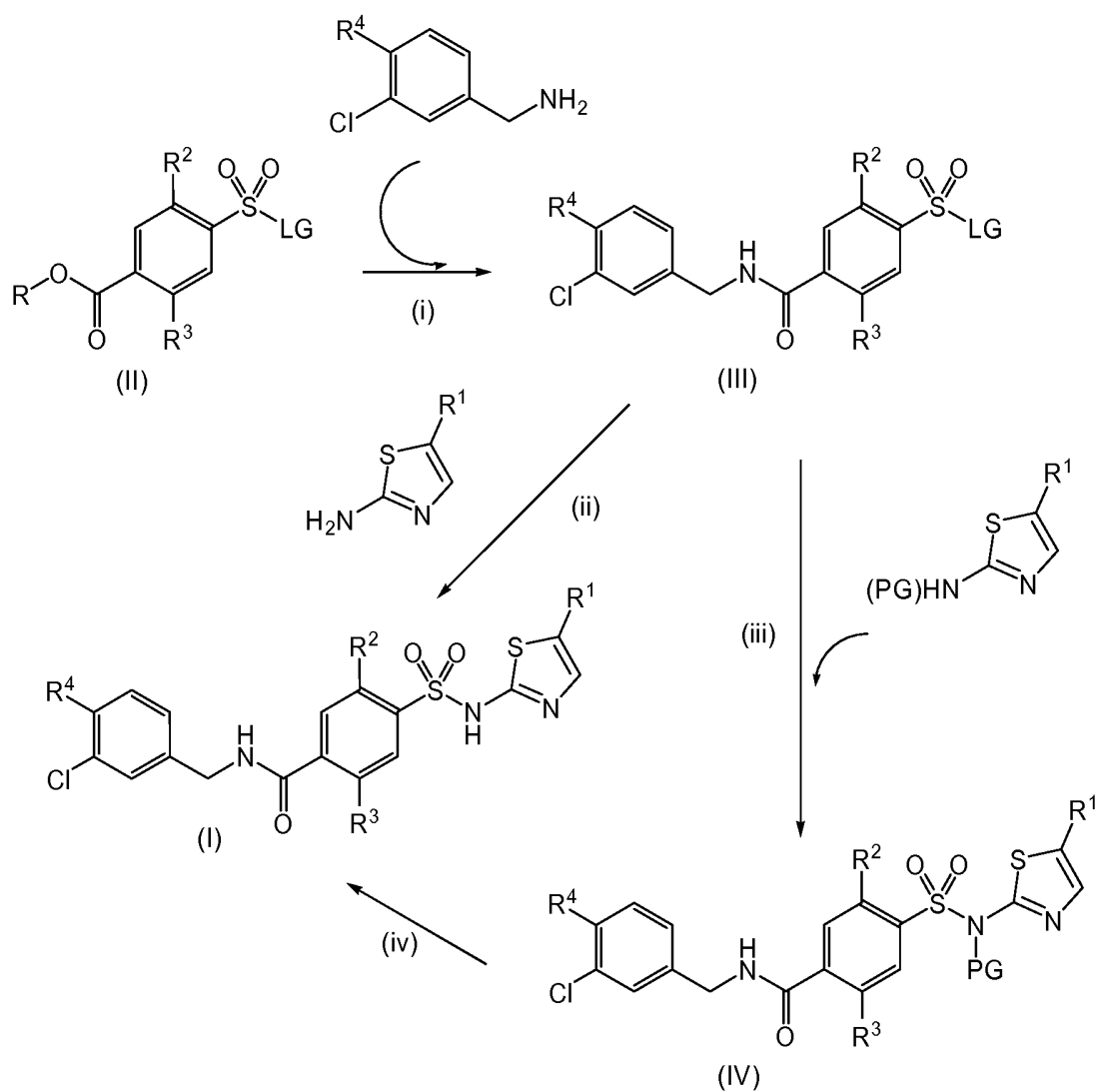
All of the compounds of the invention can be prepared by the procedures described in the general methods presented below or by the specific methods described in the Examples section and the Preparations section, or by routine modifications thereof. The present invention also encompasses any one or more of these processes for preparing the compounds of invention, in addition to any novel intermediates used therein.

In the following general methods, R^1 , R^2 , R^3 and R^4 are as previously defined for a compound of the invention unless otherwise stated.

The routes below, including those mentioned in the Examples and Preparations, illustrate methods of synthesising the compounds of the invention. The skilled person will appreciate that the compounds of the invention, and intermediates thereof, could be made by methods other than those specifically described herein, for example by adaptation of the described methods or by modification of methods known in the art. Examples of suitable guides to synthesis, functional group interconversions, use of protecting groups, etc., are: "Comprehensive Organic Transformations" by RC Larock, VCH Publishers Inc. (1989); "Advanced Organic Chemistry" by J. March, Wiley Interscience (1985); "Designing Organic Synthesis" by S Warren, Wiley Interscience (1978); "Organic Synthesis – The Disconnection Approach" by S Warren, Wiley Interscience (1982); "Guidebook to Organic Synthesis" by RK Mackie and DM Smith, Longman (1982); "Protective

Groups in Organic Synthesis” by TW Greene and PGM Wuts, John Wiley and Sons, Inc. (1999); “Protecting Groups” by PJ, Kocienski, Georg Thieme Verlag (1994); and any updated versions of said standard works.

Compounds of the invention, schematically shown as compounds of formula (I), may be prepared from compounds of formula (IV) or (III) by the process illustrated in Scheme 1.



Scheme 1

PG is a suitable nitrogen protecting group, preferably 2, 4-dimethoxybenzyl

R is H, (C₁-C₁₀)alkyl, aryl, or aryl(C₁-C₂)alkyl

LG is a suitable leaving group for example Cl or OR'', where R'' is (C₁-C₁₀)alkyl, aryl or aryl(C₁-C₂)alkyl.

When R is H, compounds of formula (III) may be prepared from compounds of formula (II) according to reaction step (i), an amide coupling between the benzylamine and the acid chloride formed from compounds of formula (II) in the presence of excess organic base such as triethylamine, pyridine, 2, 6-lutidine or Hunig's base, in a suitable solvent, at temperatures of -78°C to room temperature. The acid chloride may be prepared by reaction of a compound of formula (II) with a suitable agent such as oxalyl chloride-catalytic DMF or thionyl chloride. Typical conditions comprise oxalyl chloride-catalytic DMF in DCM at 0°C.

When LG is OR'' a subsequent reaction with the appropriate alcohol R''OH under basic conditions is required. Typical conditions comprise pentafluorophenol in the presence of Et₃N in DCM at room temperature.

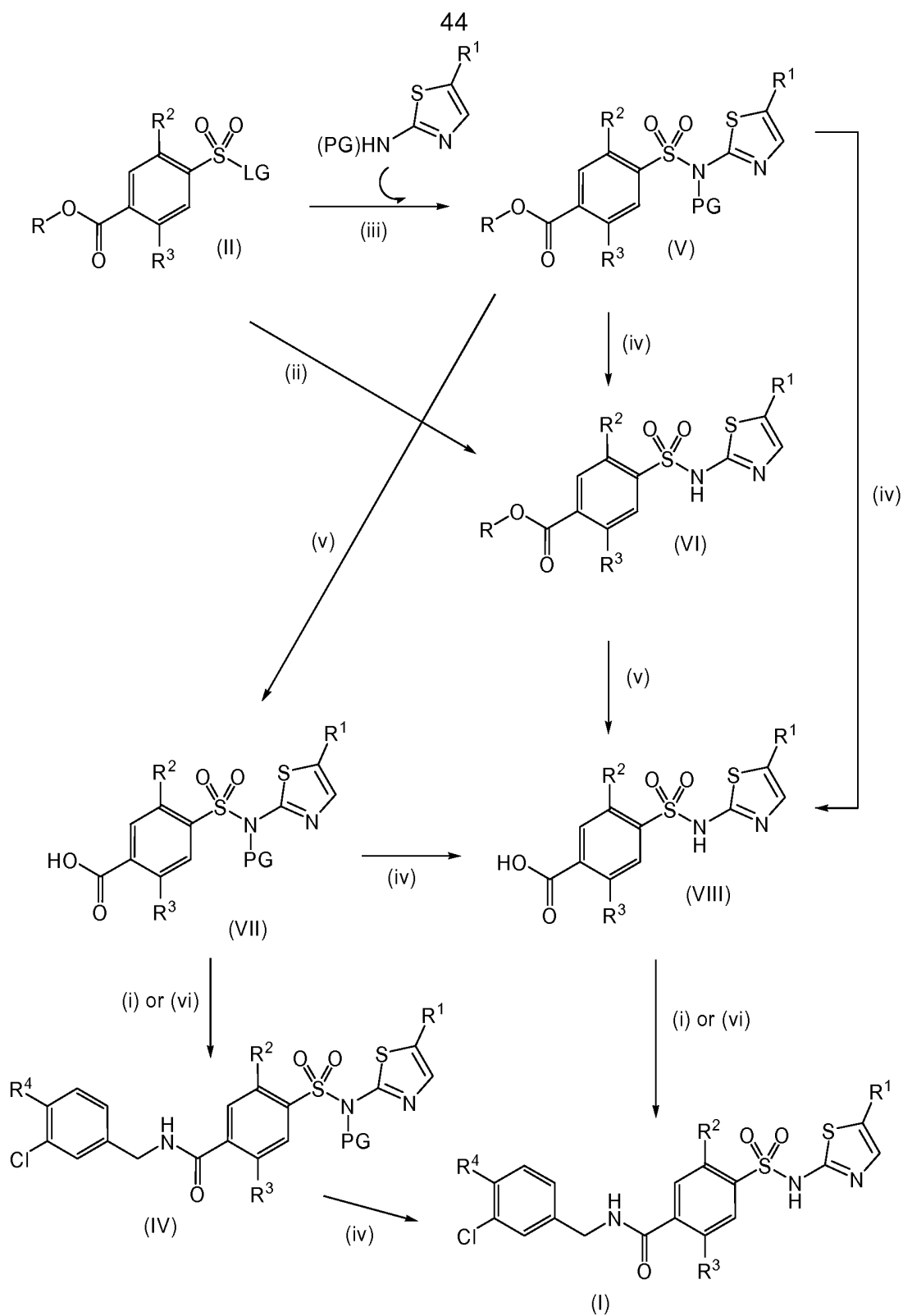
Alternatively compounds of formula (III) may be prepared from compounds of formula (XVII), as shown in Scheme 4 illustrated below.

Compounds of the invention, schematically shown as compounds of formula (I), may be prepared from compounds of formula (III) according to reaction step (ii), displacement of a leaving group with the thiazolamine under basic reaction conditions, for example, pyridine, triethylamine, DABCO or Hunig's base, optionally in the presence of a co-solvent such as DCM, at temperatures of 0 to 60°C. Typical conditions comprise reaction in pyridine at room temperature for 16 hours.

Compounds of the formula (IV) may be prepared from compounds of the formula (III) according to reaction step (iii), displacement of a leaving group with a protected thiazolamine. Any suitable nitrogen protecting group may be used (as described in "Protecting Groups in Organic Synthesis" 3rd edition T.W. Greene and P.G. Wuts, Wiley-Interscience, 1999). Common nitrogen protecting groups (PG) suitable for use in this step include tert-butoxycarbonyl (t-Boc) (which is readily removed by treatment with an acid such as trifluoroacetic acid or hydrogen chloride in an organic solvent such as dichloromethane or 1,4-dioxane), and benzyl (which is readily removed by hydrogenation in the presence of a suitable catalyst, or by treatment with 1-chloroethyl chloroformate). Step (iii) is carried out in the presence of a strong base, for example LiHMDS or NaH in a suitable solvent such as THF. Typical conditions comprise LiHMDS in THF at temperatures of -78 to 0°C. Typically PG is 2, 4-dimethoxybenzyl.

Compounds of the invention, schematically shown as compounds of formula (I), may be prepared from compounds of the formula (IV) according to reaction step (iv), deprotection of the N-protecting group (PG). For example if PG is a benzyl group, it can be readily removed by hydrogenation in the presence of a suitable catalyst or by treatment with 1-chloroethyl chloroformate. When PG = 2,4-dimethoxybenzyl typical deprotection conditions comprise HCl in an appropriate solvent such as dioxane, ether, water or TFA in DCM at room temperature.

Compounds of the invention, schematically shown as compounds of formula (I), may be prepared from compounds of formula (IV) or (VIII) by the process illustrated in Scheme 2.



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Scheme 2

PG is a suitable nitrogen protecting group, preferably 2, 4-dimethoxybenzyl

R is H, (C₁-C₁₀)alkyl, aryl or aryl(C₁-C₂)alkyl

LG is a suitable leaving group for example Cl or OR'', where R'' = H, (C₁-C₁₀)alkyl, aryl(C₁-C₂)alkyl.

Compounds of formula (V) can be prepared from compounds of formula (II) according to reaction step (iii) as previously described.

Compounds of formula (VI) may be prepared from compounds of formula (V) according to reaction step (iv) as previously described.

When R is not H compounds of formula (VI) may be prepared from compounds of formula (II) according to reaction step (ii) as previously described.

When R is H compounds of formula (V) = compounds of formula (VII).

When R is not H compounds of formula (VII) may be prepared from compounds of formula (V) according to reaction step (v), ester hydrolysis using conventional procedures, typically under aqueous basic conditions, for example in the presence of sodium hydroxide, potassium hydroxide or lithium hydroxide in an inert solvent such as methanol, ethanol, ethylene glycol, THF, DME, and 1,4-dioxane. Preferred conditions comprise aqueous sodium or lithium hydroxide in dioxane or methanol at room temperature.

When R is H compounds of formula (VIII) can be prepared from compounds of formula (V) according to reaction step (iv) as previously described.

When R is H compounds of formula (VI) = compounds of formula (VIII).

When R is not H compounds of formula (VIII) can be prepared from compounds of formula (VI) according to reaction step (v) as previously described.

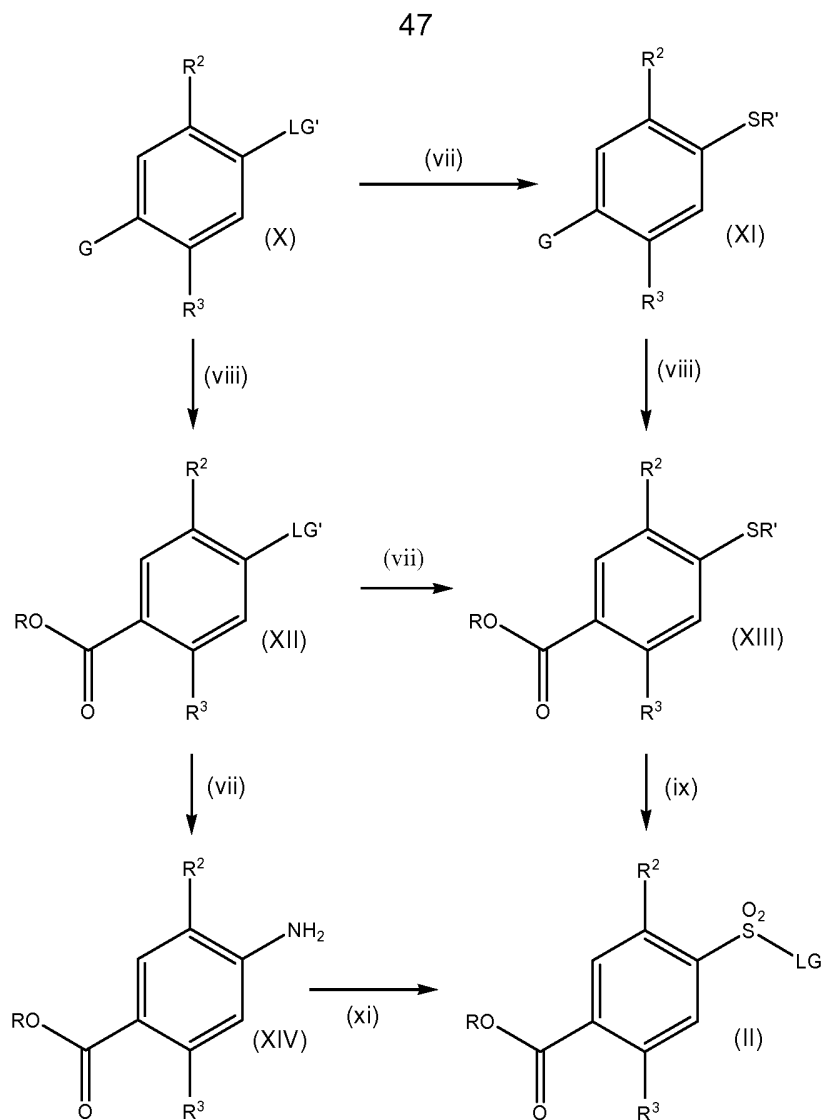
Compounds of formula (VIII) can be prepared from compounds of formula (VII) according to reaction step (iv) as previously described.

Compounds of formula (IV) may be prepared from compounds of formula (VII) according to reaction step (i), as previously described, or by reaction step (vi) an amide coupling with the benzylamine via activation of the carboxylic acid by a suitable agent such as HBTU, WSCDI or DCC, optionally in the presence of a catalyst for example HOBT or HOAT, and optionally in the presence of a tertiary amine base for example *N*-methylmorpholine, triethylamine or *N,N*-diisopropylethylamine in a suitable solvent such as DMF, THF, DMSO, DMA, at 10-40°C for 0.5-48 hours. Typical conditions comprise activation through HBTU in DMSO or DMF in the presence of Et₃N at room temperature for 0.5-16 hours.

Compounds of the invention, schematically shown as compounds of formula (I), may be prepared from compounds of formula (VIII) according to reaction steps (i) or (vi), as previously described.

Compounds of the invention, schematically shown as compounds of formula (I), may be prepared from compounds of formula (IV) according to reaction step (iv), as previously described.

Compounds of formula (II) may be prepared from compounds of formula (XIV) or (XIII) by the process illustrated in Scheme 3.

**Scheme 3**

LG and LG' are each independently a suitable leaving group, for example F, Cl, Br or OR'', where R'' = (C₁-C₁₀)alkyl, aryl, aryl(C₁-C₂)alkyl

R is H, (C₁-C₁₀)alkyl, aryl or aryl(C₁-C₂)alkyl

G is a group capable of a functional group interconversion to an acid, for example CH₃, CN.

Compounds of formula (II) where R² and R³ are both hydrogen are commercially available.

Compounds of the formula (X) are commercially available

Compounds of formula (XI) may be prepared from compounds of formula (X) according to reaction step (vii), displacement of a leaving group with a sulphur nucleophile for example benzylmercaptan, under basic reaction conditions for example in the presence of potassium carbonate, cesium carbonate or Et_3N , in a suitable solvent, for example DMSO, DMF. Typical conditions comprise benzylmercaptan in the presence of cesium carbonate in DMSO at 70-80°C for 3 hours.

Compounds of formula (XII) may be prepared from compounds of formula (X) according to reaction step (viii) a functional group interconversion to afford an acid. When G is CH_3 , an oxidation reaction is carried out using an appropriate oxidising agent, for example ceric ammonium nitrate or chromyl chloride. Typical conditions comprise excess potassium permanganate in the presence of excess aqueous KOH at 90°C for 3-4 hours. When G is CN, a hydrolysis reaction is carried out using conventional procedures, under basic or acidic conditions, for example in the presence of sodium hydroxide and hydrogen peroxide or sulphuric acid. Typical conditions comprise refluxing in concentrated hydrochloric acid or in sodium hydroxide. Alternatively, compounds of formula (XII) may be commercially available.

Compounds of the formula (XIII) may be prepared from compounds of the formula (XII) according to reaction step (vii) or from compounds of the formula (XI) according to reaction step (viii) as previously described.

Compounds of the formula (XIV) may be prepared from compounds of the formula (XII), preferably when R = H, according to reaction step (x), displacement of LG' with an ammonia source, often at elevated temperatures and pressure.

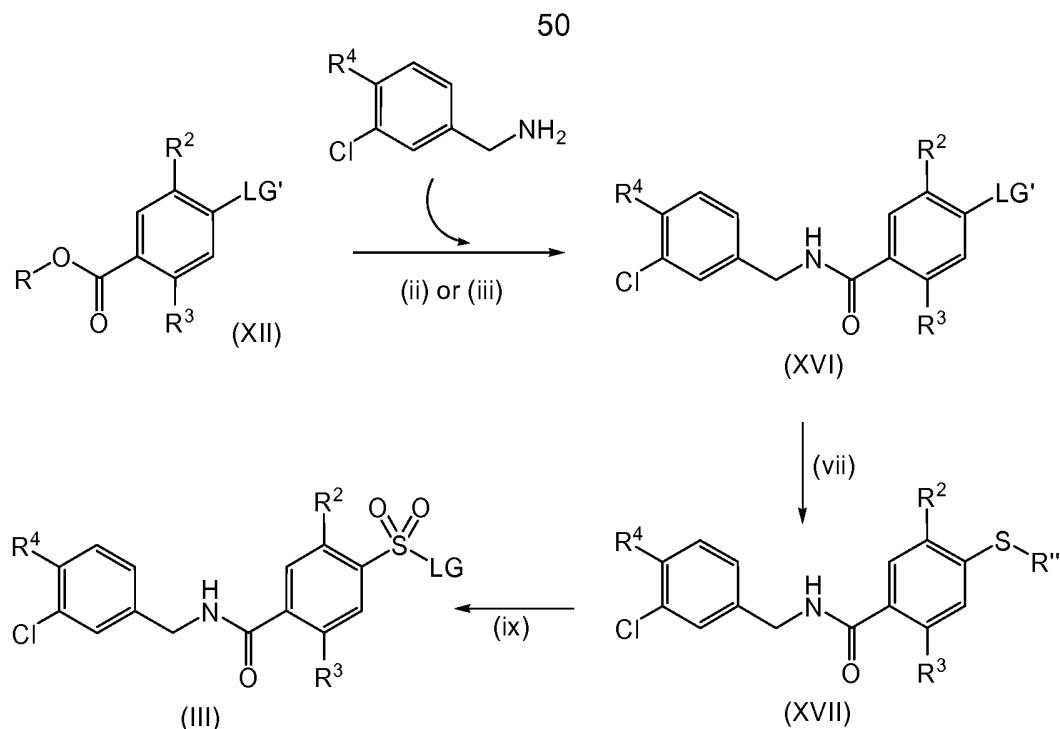
Typical conditions comprise ammonia in methanol at 180°C in an autoclave for 3-4 hours.

Compounds of formula (XIV) may be prepared by the skilled person from alternate starting materials for example reduction of the corresponding nitro compound.

Compounds of the formula (II) may be prepared from compounds of the formula (XIV) according to reaction step (xi), a diazotisation using an appropriate source of nitrous acid, for example $\text{H}_2\text{SO}_4/\text{HNO}_3$, followed by displacement of the intermediate diazonium salt with sulphur dioxide in the presence of a copper catalyst and chloride source. Typical conditions comprise sodium nitrite in HCl followed by sulphur dioxide in the presence of copper (I) chloride in acetic acid. When LG is OR'', a subsequent reaction with the appropriate alcohol R''OH under basic conditions is required. Typical conditions comprise pentafluorophenol in the presence of Et_3N in DCM at room temperature.

When LG is Cl, compounds of formula (II) may be prepared from compounds of formula (XIII) according to reaction step (ix), an oxidation to the sulfonyl chloride using an appropriate agent such as acetic acid/chlorine or aq bleach/HCl. Typical conditions comprise aq bleach/HCl at 0°C. When LG is OR'', a subsequent reaction with the appropriate alcohol R''OH under basic conditions is required. Typical conditions comprise pentafluorophenol in the presence of Et_3N in DCM at room temperature.

When LG is Cl, compounds of formula (III) may be prepared from compounds of formula (XVII) by the process illustrated in Scheme 4.

**Scheme 4**

LG' is a suitable leaving group for example F, Cl, Br or OR'' , where R'' = alkyl
 R is H, (C_1-C_{10}) alkyl, aryl, aryl(C_1-C_2)alkyl.

Compounds of the formula (XII) are commercially available or are prepared as described for step (viii) of Scheme 3.

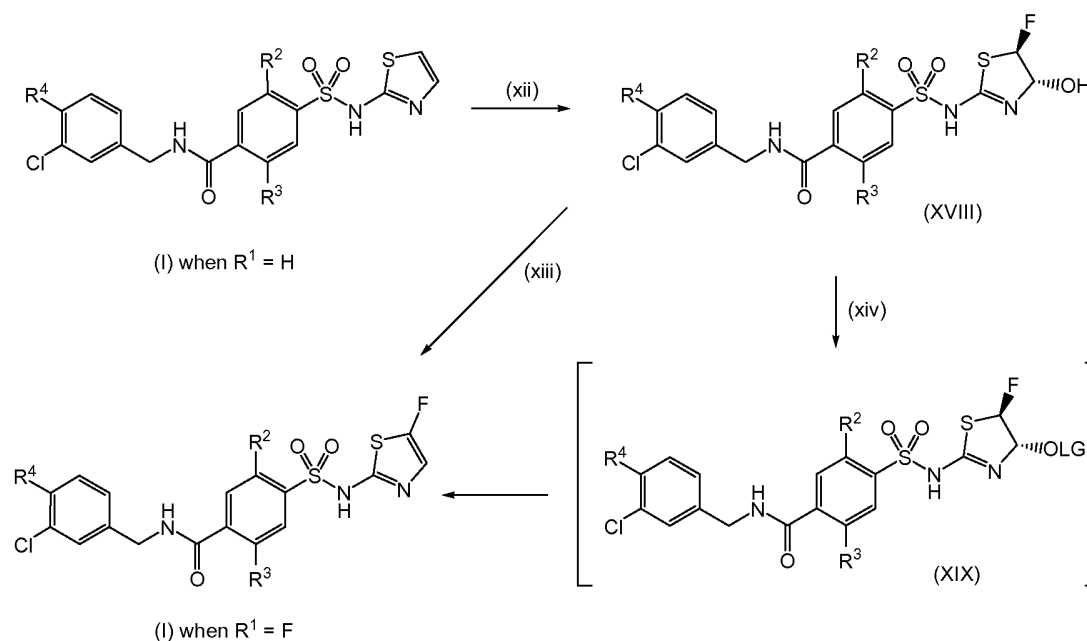
Compounds of the formula (XVI) may be prepared from compounds of the formula (XII) according to reaction step (ii) or (iii) as previously described.

Compounds of the formula (XVII) may be prepared from compounds of the formula (XVI) according to reaction step (vii) as previously described.

When LG is Cl, compounds of the formula (III) may be prepared according to reaction step (ix), an oxidation to the sulfonyl chloride using an appropriate agent such as acetic acid/chlorine or aqueous bleach/HCl. Typical conditions comprise aqueous bleach/HCl at 0°C . When LG is OR'' , a subsequent reaction with the

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appropriate alcohol R''OH under basic conditions is required. Typical conditions comprise pentafluorophenol in the presence of Et₃N in DCM at room temperature



Scheme 5

LG is a suitable leaving group, for example acetyl.

Structures for the compounds of formula (XVIII) and (XIX) are tentatively assigned as the *trans* isomers through comparison with literature methods and data comparison (*J. Chem. Soc., Perkin Trans. 1*, 1978, 1169).

Compounds of formula (I), when R¹ is F, may be prepared *via* the processes described previously (i.e. sulphonamide bond formations using 2-amino-4-fluorothiazole). Preferably, compounds of formula (I), when R¹ is F, may be prepared from compounds of formula (I), when R¹ is H, by the process illustrated in Scheme 5.

Compounds of formula (XVIII) may be prepared from compounds of formula (I), when R¹ is H, according to reaction step (xii): electrophilic fluorination of the

thiazole ring. A suitable electrophilic fluorinating agent such as Selectfluor™ may be used together with a suitable solvent such as acetonitrile or DMF at temperatures of 0 to 70°C. Typical conditions comprise Selectfluor™ in acetonitrile/water (1:1) at 70°C.

Compounds of the invention, schematically shown as compounds of formula (I), when R¹ is F may be prepared from compounds of formula (XVIII) according to reaction step (xiii): dehydration of a fluoro-hydrin moiety. Step (xiii) may be carried out in the presence of base or acid or with an appropriate dehydrating agent such as Burgess reagent.

Alternatively compounds of the invention, schematically shown as compounds of formula (I), when R¹ is F, may be prepared from intermediates of formula (XIX) according to reaction step (xiv): activation of the hydroxyl group to form a suitable leaving group such as O-acetyl and subsequent elimination under basic or acidic conditions. Typical conditions comprise acetic anhydride and triethylamine in DCM at room temperature.

The skilled person will appreciate that many of the aforementioned intermediates could be made by methods other than those specifically described herein, for example by alternate order of reaction steps. For example, compounds of formula (VIII) could be accessed from compounds of the formula (X), by conversion to a sulfonyl chloride and subsequently sulfonamide prior to functional group interconversion to an acid, using the chemical steps already described.

When preparing compounds of formula of the invention, schematically shown as compounds of formula (I), in accordance with the invention, it is open to a person skilled in the art to routinely select the best order of steps with which to synthesise the intermediates, and to choose the form of the intermediate compounds which provides the best combination of features for this purpose.

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Such features include the melting point, solubility, processability and yield of the intermediate form and the resulting ease with which the product may be purified on isolation. The skilled person may undertake the synthetic steps described above in any suitable order in order to arrive at the compounds of the invention.

Referring to the general methods above, it will be readily understood to the skilled person that where protecting groups are present, these will be generally interchangeable with other protecting groups of a similar nature, e.g. where an amine is described as being protected with a *tert*-butoxycarbonyl group, this may be readily interchanged with any suitable amine protecting group. Suitable protecting groups are described in 'Protective Groups in Organic Synthesis' by T. Greene and P. Wuts (3rd edition, 1999, John Wiley and Sons).

The present invention also relates to novel intermediate compounds as defined above, all salts, solvates and complexes thereof and all solvates and complexes of salts thereof as defined hereinbefore for benzamide derivatives of the invention. The invention includes all polymorphs of the aforementioned species and crystal habits thereof. The invention includes the use of compounds of the invention, schematically shown as compounds of formula (I), when R¹ is hydrogen, as intermediates in the preparation of compounds of the invention, when R¹ is fluoro.

The following Examples illustrate the preparation of compounds of the invention.

NMR

¹H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The mass spectra (MS) were recorded using either

electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI). The following abbreviations have been used for common solvents: CDCl_3 , deuteriochloroform; $\text{D}_6\text{-DMSO}$, deuterodimethylsulphoxide; CD_3OD , deuteromethanol; THF, tetrahydrofuran. LCMS indicates liquid chromatography mass spectrometry (R_t = retention time). Where ratios of solvents are given, the ratios are by volume.

LCMS

6 minute LC-MS gradient and instrument conditions

Acid run:

A: 0.1 % formic acid in water

B: 0.1 % formic acid in acetonitrile

Column: C18 phase Phenomenex Gemini 50 x 4.6mm with 5 micron particle size

Gradient: 95-5% A over 3min, 1 min hold, 1ml/min

UV: 210nm - 450nm DAD

Temperature: 50°C

2 minute LC-MS gradient and instrument conditions

Acid run:

A: 0.1 % formic acid in water

B: 0.1 % formic acid in acetonitrile

Column: C18 phase Fortis Pace 20 x 2.1mm with 3 micron particle size

Gradient: 70-2% A over 1.8min, 0.2 min hold, 1.8ml/min

UV: 210nm - 450nm DAD

Temperature: 75°C

5 minute LC-MS gradient and instrument conditions

Acid run:

A 0.0375% TFA in water

B 0.01875% TFA in acetonitrile

Column Ymc ODS-AQ 50mm x 2mm with 5 micron particle size

55

Gradient: 90-10% A over 4.7min, 1 min hold, 0.8mL/min

Temperature: 50°C

C18 30 minute method LC-MS gradient and instrument conditions

A: 0.1% formic acid in H₂O

B: 0.1% formic acid in MeCN

Column: Phenomenex C18 phase Gemini 150 x 4.6mm with 5 micron particle size

Gradient: 98-2% A over 18min, 2 min hold, 1ml/min

UV: 210nm - 450nm DAD

Temperature: 50°C

Phenyl Hexyl 30 minute method LC-MS gradient and instrument conditions

A: 10 mM ammonium acetate in H₂O

B: 10 mM ammonium acetate in MeOH

Column: Phenomenex Phenyl Hexyl 150 x 4.6mm with 5 micron particle size

Gradient: 98-2% A over 18min, 2 min hold, 1ml/min

UV: 210nm - 450nm DAD

Temperature: 50°C

Unless otherwise noted, LCMS conditions were run according to the 2 minute LCMS gradient.

Unless otherwise provided herein:

CDI means N,N'-carbonyldiimidazole;

WSCDI means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;

DCC means N,N'-dicyclohexylcarbodiimide;

HOAT means 1-hydroxy-7-azabenzotriazole;

HOBT means 1-hydroxybenzotriazole hydrate;

HBTU means O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium

hexafluorophosphate;

TBTU means O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium

tetrafluoroborate

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Hünig's base means N-ethyldiisopropylamine;

Et₃N means triethylamine;

DMAP means 4-dimethylaminopyridine;

LiHMDS means lithium bis(trimethylsilyl)amide;

Boc means *tert*-butoxycarbonyl;

CBz means benzyloxycarbonyl;

THF means tetrahydrofuran,

DMSO means dimethyl sulphoxide,

DCM means dichloromethane,

DMF means N,N-dimethylformamide;

AcOH means acetic acid,

TFA means trifluoroacetic acid

HCl means hydrochloric acid

DABCO means 1,4-diazabicyclo[2.2.2]octane

NaH means sodium hydride

SelectFluor® means 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane
bis(tetrafluoroborate)

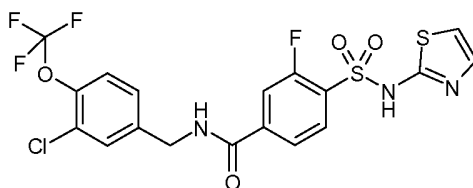
EtOAc means ethyl acetate

MeOH means methanol

TBME means *tert*-butyl methyl ether

Example 1

N-[3-chloro-4-(trifluoromethoxy)benzyl]-3-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide



To a suspension of 3-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoic acid

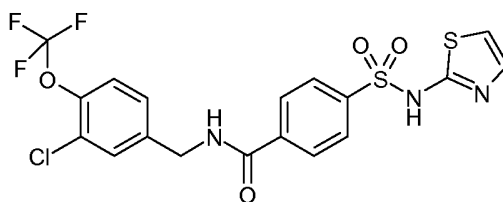
57

(preparation 15, 2.88g, 9.54mmol) and 1-[3-chloro-4-(trifluoromethoxy)phenyl]methanamine (preparation 16, 3.00g, 11.4mmol) and Et₃N (4.81ml, 34.5mmol) in DMSO (30mL) was added HBTU (4.34g, 34.5mmol) and the mixture stirred at room temperature for 18 hours. The reaction was then diluted with EtOAc (100ml) before washing with water (100mL) and brine (3 x 100mL). The EtOAc layer was dried (Na₂SO₄), filtered and concentrated *in vacuo* leaving a brown solid (6.38g). The crude product was triturated with MTBE, dried *in vacuo* and stirred in EtOAc for 20 minutes and the resulting off-white solid filtered off and dried *in vacuo* overnight to provide the title compound (3.97g, 7.8mmol).

¹H NMR (d₆-DMSO): 4.50 (d, 2 H), 6.90 (d, 1 H), 7.30 (d, 1 H), 7.40 (d, 1 H), 7.50 (d, 1 H), 7.60 (s, 1 H), 7.75 (s, 1 H), 7.80 (d, 1 H), 7.90 (t, 1 H), 9.25 (t, 1 H). LCMS Rt = 1.49min. MS m/z 510 [M+H]⁺

Example 2

N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide



Prepared according to example 1 using 4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoic acid (preparation 4, 2.71g, 9.55mmol) and 1-[3-chloro-4-(trifluoromethoxy)phenyl]methanamine (preparation 16, 3.00g, 11.4mmol) to provide the title compound as a white solid (3.65g, 7.4mmol).

¹H NMR (d₆-DMSO): 4.50 (d, 2 H), 6.80 (d, 1 H), 7.25 (d, 1 H), 7.40 (d, 1 H), 7.50 (d, 1 H), 7.60 (s, 1 H), 7.85 (d, 2 H), 8.00 (d, 2 H), 8.20 (m, 1 H), 12.80 (br s, 1 H)

LCMS Rt = 1.46min. MS m/z 492 [M+H]⁺

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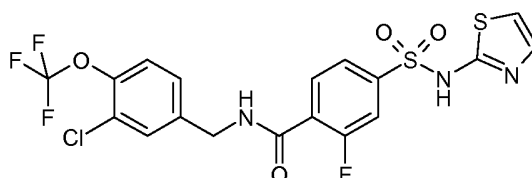
The potassium salt of N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide can also be prepared as follows:

To a suspension of N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide (Example 2, 500mg, 1.0mmol) in methyl-ethyl ketone (MEK) (15mL) at 70°C was added potassium hydroxide (63mg, 1.1mmol) and the resulting solution stirred for 1 hour at 70°C. The mixture was then cooled to room temperature with stirring over 18 hours before concentration *in vacuo*. The crude was recrystallised from acetone/toluene (~1:1) to provide potassium salt of the title compound (400mg, 0.74mmol).

¹H NMR (d₆-DMSO): 4.46 (d, 2H), 6.42 (d, 1H), 6.90 (d, 1H), 7.39 (d, 1H), 7.50 (d, 1H), 7.59 (s, 1H), 7.77-7.86 (m, 4H), 9.10 (t, 1H).

Example 3

N-[3-chloro-4-(trifluoromethoxy)benzyl]-2-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide



Prepared according to example 1 using 2-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoic acid (preparation 10, 2.23g, 7.39mmol) and 1-[3-chloro-4-(trifluoromethoxy)phenyl]methanamine (preparation 16, 2.00g, 8.86mmol). Purification was accomplished *via* column chromatography through a short pad of silica gel eluting with EtOAc:MeOH:NH₃ (95:5:0.5) to provide the title compound as an off-white solid (1.41g, 2.76mmol).

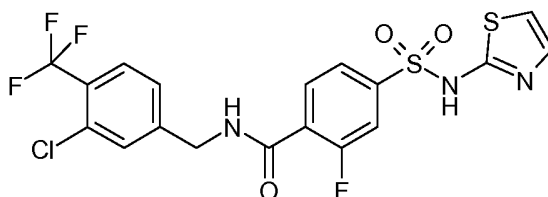
¹H NMR (d₆-DMSO): 4.50 (d, 2 H), 6.85 (d, 1 H), 7.25 (d, 1 H), 7.40 (d, 1 H), 7.55 (d, 1 H), 7.60-7.65 (m, 2 H), 7.70 (d, 1 H), 7.80 (t, 1 H), 9.05 (t, 1 H)

LCMS Rt = 1.49min. MS m/z 510 [M+H]⁺

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Example 4

N-[3-chloro-4-(trifluoromethyl)benzyl]-2-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide



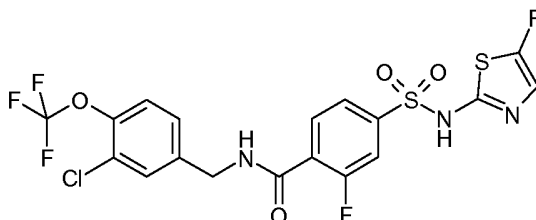
Prepared according to example 1 using 2-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoic acid (preparation 10, 150mg, 0.50mmol) and 1-[3-chloro-4-(trifluoromethyl)phenyl]methanamine (140mg, 0.57mmol). Purification was accomplished *via* column chromatography on silica gel (12g) eluting with DCM/MeOH/AcOH (95:5:0.5) followed by trituration of concentrated product containing fractions with DCM to provide the title compound as a white solid (100mg, 0.20mmol).

¹H NMR (d₆-DMSO): 4.55 (d, 2 H), 6.90 (d, 1 H), 7.30 (d, 1 H), 7.45 (d, 1 H), 7.65 (m, 2 H), 7.70 (d, 1 H), 7.75 (d, 1 H), 7.80 (t, 1 H) 9.10 (t, 1 H), 12.90 (s, 1 H)

LCMS Rt = 1.49min. MS m/z 494 [M+H]⁺

Example 5

N-[3-chloro-4-(trifluoromethoxy)benzyl]-2-fluoro-4-[(5-fluoro-1,3-thiazol-2-yl)amino]sulfonyl}benzamide



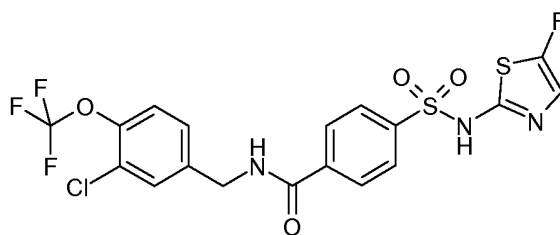
To a suspension of rac-N-[3-chloro-4-(trifluoromethoxy)benzyl]-2-fluoro-4-([(4R*,5S*)-5-fluoro-4-hydroxy-4,5-dihydro-1,3-thiazol-2-yl]amino)sulfonyl}benzamide (preparation 21, 1.4g, 2.56mmol) in DCM (30mL)

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and Et₃N (3.6mL, 26mmol) was added acetic anhydride (1mL, 10mmol) and the solution stirred at room temperature for 18 hours. The mixture was quenched with 2N HCl (aq) (70mL) before washing the organic layer with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to a brown oil. This was re-dissolved in EtOAc(10mL) and eluted through a short pad of silica gel with EtOAc (250mL) before concentrating *in vacuo* to provide a cream foam. Final purification was accomplished *via* column chromatography on silica gel eluting with DCM:MeOH (98:2) to furnish a white foam - azeotroped with DCM and heptane to provide the title compound as a white solid (360mg, 0.68mmol).
1H NMR (d₆-DMSO): 4.50 (d, 2 H), 7.35 (s, 1 H), 7.40 (d, 1 H). 7.55 (d, 1 H), 7.60 (s, 1 H), 7.65-7.70 (m, 2 H), 7.80 (t, 1 H), 9.05 (t, 1 H)
LCMS Rt = 1.57min. MS m/z 528 [M+H]⁺

Example 6

N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-([(5-fluoro-1,3-thiazol-2-yl)amino)sulfonyl]benzamide



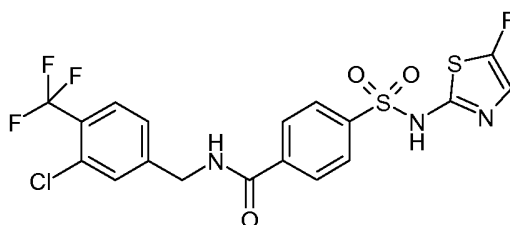
To a suspension of rac-N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-([(4R*,5S*)-5-fluoro-4-hydroxy-4,5-dihydro-1,3-thiazol-2-yl]amino)sulfonyl]benzamide (preparation 18, 195mg, 0.369mmol) in DCM (3mL) was added Et₃N (0.50mL, 3.60mmol) followed by acetic anhydride (0.14mL, 1.50mmol) and the mixture was stirred at room temperature for 18 hours. The mixture was washed with 2N HCl (aq) (10mL), dried (Na₂SO₄) and purified *via* column chromatography on silica gel (12g) eluting with DCM:MeOH (95:5). The product containing fractions were concentrated before trituration with DCM to provide the title compound as an off-white solid (61mg, 0.11mmol).

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¹H NMR (d₆-DMSO): 4.50 (d, 2 H), 7.35 (s, 1 H), 7.40 (d, 1 H), 7.55 (d, 2 H), 7.60 (s, 1 H), 7.90 (d, 2 H), 8.00 (d, 2 H), 9.25 (t, 1 H)
LCMS Rt = 1.53min. MS m/z 510 [M+H]⁺

Example 7

N-[3-chloro-4-(trifluoromethyl)benzyl]-4-[(5-fluoro-1,3-thiazol-2-yl)amino]sulfonyl}benzamide



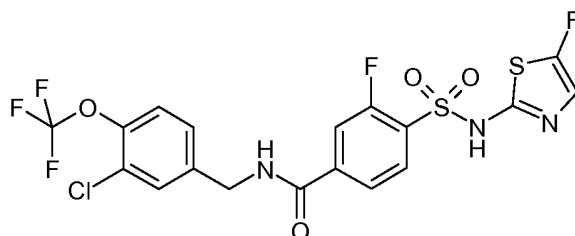
To a suspension of rac-N-[3-chloro-4-(trifluoromethyl)benzyl]-4-([(4R*,5S*)-5-fluoro-4-hydroxy-4,5-dihydro-1,3-thiazol-2-yl]amino)sulfonyl}benzamide (preparation 19, 165mg, 0.32mmol) in DCM (3mL) was added Et₃N (0.44mL, 3.20mmol) followed by acetic anhydride (0.11mL, 1.30mmol) and the mixture was stirred at room temperature for 18 hours. The mixture was then concentrated *in vacuo* before trituration with DCM to provide the title compound as a pale orange solid (53mg, 0.10mmol).

¹H NMR (d₆-DMSO): 4.55 (d, 2 H), 7.35 (s, 1 H), 7.45 (d, 1 H), 7.65 (s, 1 H), 7.80 (d, 1 H), 7.90 (d, 2 H), 8.00 (d, 2 H), 9.25 (t, 1 H)
LCMS Rt = 1.51min. MS m/z 494 [M+H]⁺

Example 8

N-[3-chloro-4-(trifluoromethoxy)benzyl]-3-fluoro-4-[(5-fluoro-1,3-thiazol-2-yl)amino]sulfonyl}benzamide

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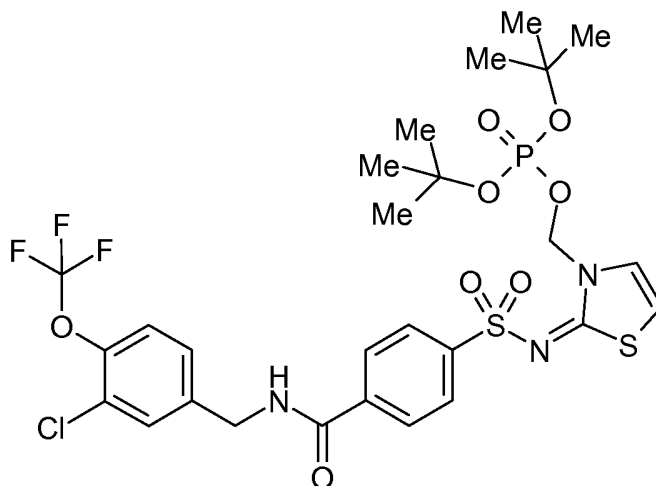
To a suspension of rac-N-[3-chloro-4-(trifluoromethoxy)benzyl]-3-fluoro-4-(([(4R*,5S*)-5-fluoro-4-hydroxy-4,5-dihydro-1,3-thiazol-2-yl]amino)sulfonyl)benzamide (preparation 20, 405mg, 0.74mmol) in DCM (6mL) was added Et₃N (1.00mL, 7.17mmol) followed by acetic anhydride (0.28mL, 3.00mmol) and the mixture was stirred at room temperature for 18 hours. The mixture was then concentrated *in vacuo* before trituration from DCM to provide the title compound as a pale orange solid (79mg, 0.15mmol).

¹H NMR (d₆-DMSO): 4.50 (d, 2 H), 7.40 (s and d, 2 H), 7.55 (d, 1 H), 7.60 (s, 1 H), 7.80 (d and s, 2 H), 7.95 (t, 1 H), 9.30 (t, 1 H)

LCMS Rt = 1.57min. MS m/z 528 [M+H]⁺

Example 9

di-tert-butyl [(2Z)-2-{[(4-{[3-chloro-4-(trifluoromethoxy)benzyl]carbonyl}phenyl)sulfonyl]imino}-1,3-thiazol-3(2H)-yl]methyl phosphate



N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide (Example 2, 600 mg) was stirred at room temperature in dimethylformamide (10 ml) with caesium carbonate (1200 mg) and di-*tert*-butyl chloromethyl phosphate (480 mg) and then heated at 60°C for 18 hours. The reaction mixture was cooled and partitioned between ethyl acetate (50 ml), methyl-*t*-butyl ether (50ml) and water (60ml), the pH of the aqueous was adjusted to 7 by adding a pellet of solid carbon dioxide. The organic layer was dried over anhydrous sodium sulphate, filtered and the solvents removed *in vacuo* to give the crude product as a yellow oil which crystallized on standing.

MS m/z = 712/714 (M-H)-

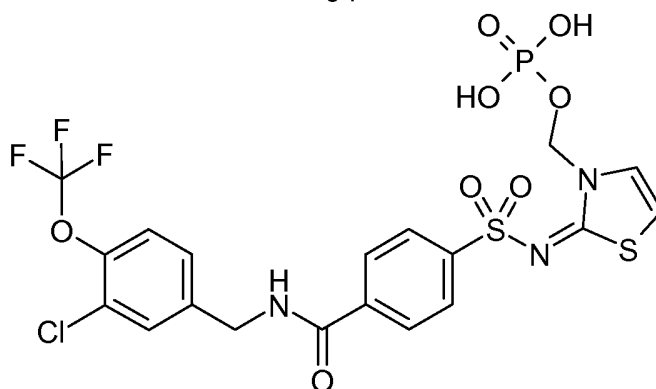
The crude product was recrystallised from EtOAc to give the pure title product as a white powder (290 mg) and a second crop was obtained by evaporating the liquors and triturating the residue with methyl *t*-butyl ether to give a white powder (106 mg).

¹HNMR (CDCl₃): δ 1.39 (s, 18H), 4.64 (d, 2H), 5.68 (d, 2H), 6.47 (s, 1H), 6.71 (t, 1H), 7.20 (s, 1H), 7.80 (s, 2H), 7.48 (s, 1H), 7.87 (d, 2H), 8.01 (d, 2H).

Example 10

[(2Z)-2-[(4-{[3-chloro-4-(trifluoromethoxy)benzyl]carbamoyl}phenyl)sulfonyl]imino}-1,3-thiazol-3(2H)-yl]methyl dihydrogen phosphate

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di-*tert*-butyl [(2*Z*)-2-[[4-[[3-chloro-4-(trifluoromethoxy)benzyl]carbamoyl]phenyl)sulfonyl]imino}-1,3-thiazol-3(2*H*)-yl]methyl phosphate (Example 9, 395 mg) was suspended in ethyl acetate (2 ml) and trifluoroacetic acid (1 ml) was added, stirred at room temperature for 75 minutes. The solvents were removed *in-vacuo* and the residue was dried under high vacuum for 3 days. The residue was recrystallised from ethyl acetate twice to give the title compound as a white powder (198 mg).

LCMS R_t =1.41 minutes, MS m/z = 602/604 $[M+H]^+$

^1H NMR (CD_3OD): δ 4.57 (s, 2H), 5.74 (d, 2H), 6.78 (s, 1H), 7.32 (s, 1H), 7.39 (s, 2H), 7.56 (s, 1H), 7.94-8.04 (m, 5H).

Example 11

Spray Dried Dispersion Formulation of N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide

A spray dried dispersion (SDD) formulation of N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide (Example 2) was prepared according to the following procedure.

To a stirred solution of N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide (Example 2) in acetone in an Erlenmeyer flask was

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added high granular grade hydroxypropylmethyl cellulose acetate succinate (HPMCAS-HG) in the weight ratios provided in table X below.

Table X

Component	Wt% of total
N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide	0.75
HPMCAS-HG	2.25
Acetone	97

The mixture was then spray dried according to the parameters outlined in Table Y.

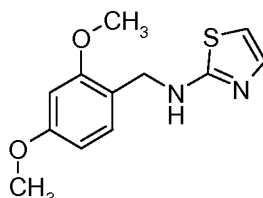
Table Y

Spray Dryer	0.5 scale spray drier'
Inlet temperature (°C)	95
Outlet temperature (°C)	45
Solution feed rate (g/min)	30
Nozzle	Pressure swirl (Schlick model 121, 0.2mm orifice)
Drying gas feed rate (g/min)	475
Product collection	Cyclone separator

The SDD material was dried a second time to remove any residual acetone using a vacuum desiccator, (-24 mmHg) for 3 to 12-hours to give the spray dried dispersion formulation.

The following Preparations illustrate the preparation of certain intermediates used to prepare the above Examples.

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Preparation 1N-(2,4-dimethoxybenzyl)-1,3-thiazol-2-amineMethod A

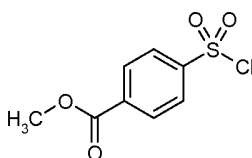
2,4 Dimethoxybenzaldehyde (25g, 150mmol), 2 aminothiazole (15.1g, 150mmol) and piperidine (150mg, 1.76mmol) were combined in dichloroethane (500mL) and the reaction mixture heated to reflux over sieves for 18 hours. The sieves were removed by filtration and the reaction mixture diluted with MeOH (300mL). Sodium borohydride (25g, 662mmol) was added portionwise and the reaction mixture heated to reflux for 2 hours. The mixture was cooled, quenched with water and the organic solvent evaporated *in vacuo*. The reaction mixture was extracted into EtOAc and the combined organic solutions extracted with 2N HCl (aq). The acidic solution was basified with potassium carbonate, re-extracted into EtOAc, dried (Na₂SO₄) and concentrated *in vacuo*. The crude material was purified by column chromatography eluting with DCM:MeOH (9:1) to yield the title compound (24g, 96mmol).

¹HNMR (d₆-DMSO): 3.7 (s, 3H), 3.8 (s, 3H), 4.3 (d, 2H), 6.5 (m, 1H), 6.6 (m, 2H), 7.0 (s, 1H), 7.2 (d, 2H), 7.7 (t, 1H).

Method B

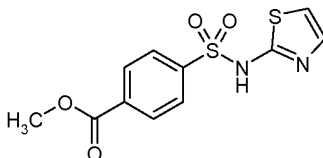
Also prepared according to Gutierrez *et al.* Tetrahedron Letters **2005**, 46(20), 3595-3597.

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Preparation 2Methyl 4-(chlorosulfonyl)benzoate

4-Chlorosulphonylbenzoic acid (15g, 68mmol) was suspended in thionyl chloride (60mL) and DCM (60mL) and the reaction mixture heated at reflux for 2 hours. The solvent was evaporated *in vacuo* and ice cold MeOH (120mL) was added to the residue. The mixture was stirred for 10 minutes in an ice bath before the addition of ice cold water (100mL). The resulting precipitate was collected by filtration to yield the title compound as a white solid (15.3g, 65mmol).

¹HNMR (CDCl₃): 4.0 (s, 3H), 8.1 (d, 2H), 8.3 (d, 2H).

Preparation 3Methyl 4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoate

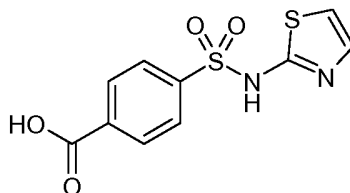
To a solution of 2-aminothiazole (141.4g, 1.4mol) in pyridine (350mL) was added methyl 4-(chlorosulfonyl)benzoate (preparation 2, 66.3g, 0.28mol) and the mixture stirred at 40°C for 18 hours. The reaction was then allowed to cool and poured into 2N HCl (aq) (300mL) and the mixture acidified to pH = 1 with 4N HCl (aq). The resulting precipitate was filtered, washed with water and dried *in vacuo* to provide the title compound as an off white solid (36.8g, 0.12mol).

¹HNMR (d₆-DMSO): 3.84 (s, 3H), 6.84 (d, 1H), 7.26 (d, 1H), 7.89 (d, 2H), 8.06 (d, 2H).

LCMS (5min) Rt = 1.48min. MS m/z 299 [M+H]⁺

Preparation 4

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4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoic acid



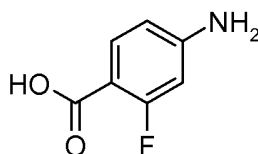
A mixture of methyl 4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoate (preparation 3, 36.8g, 0.12mol), 2N NaOH (aq) (850mL) and dioxane (170mL) were stirred at 50°C for 24 hours. The reaction was allowed to cool to room temperature and diluted with EtOAc (1000mL) before acidifying to pH = 1 with 4N HCl (aq). The resulting precipitate was filtered, washed with water and dried *in vacuo* to provide the title compound as an off white solid (25.4g, 0.09mol).

¹HNMR (d₆-DMSO): 6.84 (d, 1H), 7.26 (d, 1H), 7.87 (d, 2H), 8.04 (d, 2H).

LCMS (5min) Rt = 1.41min. MS m/z 285 [M+H]⁺

Preparation 5

4-Amino-2-fluorobenzoic acid

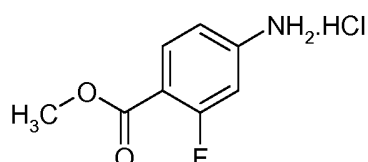


A mixture of 4-amino-2-fluorobenzonitrile (25g, 0.183mmol) and potassium hydroxide (125g, 2.23mol) in water (350mL) and industrial methylated spirit (50mL) was heated at reflux for 48 hours. The solvent was evaporated *in vacuo* and the residue diluted with water (300mL) and washed with DCM (200mL). The aqueous phase was acidified to pH = 5.5 with concentrated HCl and the resultant precipitate collected by filtration to yield the title compound as a beige solid (23.94g, 0.154mol).

¹HNMR (d₆-DMSO): 6.19 (br s, 2H), 6.19-6.35 (m, 2H), 7.51 (t, 1H).

m/z 156.02 [M+H]⁺.

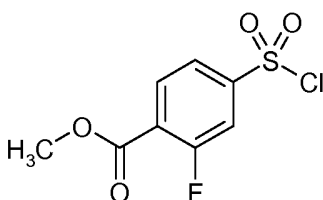
69

Preparation 6Methyl 4-amino-2-fluorobenzoate hydrochloride

4-Amino-2-fluorobenzoic acid (preparation 5, 23.9g, 0.154mol) was dissolved in MeOH (500mL), HCl gas was bubbled through the solution until the boiling point of the solution was reached. The reaction mixture was then heated at reflux for 72 hours. The solvent was evaporated to yield the title compound as a beige solid (33.2g, crude quantitative yield).

^1H NMR (d_6 -DMSO): 3.68 (s, 3H), 6.21 (br s), 6.44-6.54 (m, 2H), 7.58 (t, 1H).

LCMS (5min) Rt = 1.59min. MS m/z 170 [M+H] $^+$.

Preparation 7Methyl 4-(chlorosulfonyl)-2-fluorobenzoate

To a suspension of methyl 4-amino-2-fluorobenzoate hydrochloride (preparation 6, 33.2g, 0.154mmol) in concentrated HCl:water (140mL, 1:1) was cooled in an ice bath before addition of a solution of sodium nitrite (11.71g, 0.169mol, 1.1eq) in warm water (20mL) dropwise maintaining the temperature below 5°C. The reaction mixture was allowed to stir for 10 minutes then filtered through a pad of Celite and the resulting solid washed with water. The filtrate was then added portionwise to a solution of sulphur dioxide (49.4g, 0.771mol) and copper (1) chloride (100mg) in AcOH (120mL) maintaining the temperature below 0°C. Following complete addition the reaction was stirred for 30 minutes. The aqueous layer was extracted with DCM (3x150mL), the combined organics

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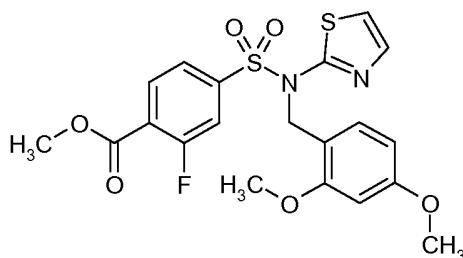
washed with saturated sodium hydrogen carbonate, water and brine, dried (MgSO_4), filtered and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel eluting with EtOAc:hexane (9:1) to yield the title compound as a red oil (19.68g, 0.078mol).

^1H NMR (CDCl_3): 4.00 (s, 3H), 7.80-7.90 (m, 2H), 8.15-8.19 (m, 1H).

MS m/z 251 $[\text{M}-\text{H}]^-$.

Preparation 8

Methyl 4-[(2,4-dimethoxybenzyl)(1,3-thiazol-2-yl)amino]sulfonyl-2-fluorobenzoate

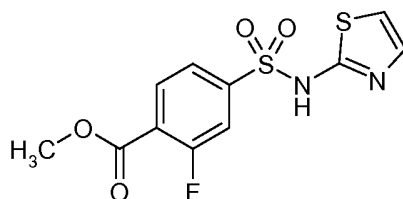


To an ice cooled solution of N-(2,4-dimethoxybenzyl)-1,3-thiazol-2-amine (preparation 1, 9.0g, 35.9mmol) in THF (80mL) was added 60% sodium hydride (2.15g, 53.9mmol) portionwise. The mixture was stirred at 0°C for 30 minutes before the addition of methyl 4-(chlorosulfonyl)-2-fluorobenzoate (preparation 7, 9.06g, 35.9mmol) and the mixture allowed to warm to room temperature and stirred for a further 1 hour. The reaction mixture was added to water (20mL) and the organics concentrated *in vacuo*. The residue was diluted with water (200mL), extracted with DCM (3 x 200mL), the combined organics dried (Na_2SO_4) and concentrated *in vacuo* to yield the title compound as an orange solid (17.1g, 36.7mmol). This material was used with no further purification.

^1H NMR (CDCl_3): 3.68 (s, 3H), 3.75 (s, 3H), 3.95 (s, 3H), 5.03 (s, 2H), 6.30-6.40 (m, 2H), 7.06 (d, 1H), 7.12 (d, 1H), 7.44 (d, 1H), 7.52-7.65 (m, 2H), 7.96-8.05 (m, 1H).

MS m/z 467 $[\text{M}+\text{H}]^+$.

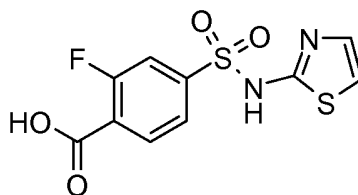
71

Preparation 9Methyl 2-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoate

Methyl 4-[[[2,4-dimethoxybenzyl)(1,3-thiazol-2-yl)amino]sulfonyl]-2-fluorobenzoate (preparation 8, 13.55g, 29.05mmol) was treated with 4N HCl (aq):dioxane (1:1, 30mL) and stirred at room temperature for 48 hours. The reaction mixture was filtered and the solid washed with MeOH before concentrating the filtrate *in vacuo* to provide the title compound (8.55g, 27.0mmol).

¹HNMR (d₆-DMSO): 3.83 (s, 3H), 6.87 (d, 1H), 7.28 (d, 1H), 7.60-7.71 (m, 2H), 7.98 (t, 1H).

LCMS (5min) Rt = 1.55min. MS m/z 317 [M+H]⁺.

Preparation 102-Fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoic acidMethod A

A mixture of methyl 4-[[[2,4-dimethoxybenzyl)(1,3-thiazol-2-yl)amino]sulfonyl]-2-fluorobenzoate (preparation 8, 10g, 21mmol) and sodium hydroxide (4.3g, 0.107mol) in THF: MeOH: water (25mL:2mL:75mL) was heated at 50°C for 4 hours. The reaction mixture was acidified to pH = 2.0 with 2N HCl (aq) and the resulting precipitate collected by filtration. The crude material was purified by

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column chromatography on silica gel eluting with 90:10:1 DCM: MeOH: ammonia to yield the title compound as a yellow solid (706mg, 2.33mmol).

Method B

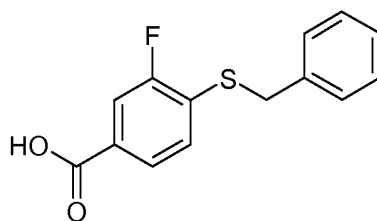
A suspension of methyl 2-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoate (preparation 9, 8.55g, 27.0mmol) in 2.5N NaOH (aq) (43mL) and dioxane (12mL) was heated to 50°C for 2 hours. The reaction was cooled to room temperature before extraction with EtOAc (50mL). The aqueous layer was then acidified to pH = 1 with c.HCl before extraction with EtOAc (3 x 100mL). These organic layers were concentrated *in vacuo*, redissolved in hot MeOH and filtered. The filtrate was concentrated and dried *in vacuo* to provide the title compound as a yellow solid (5.0g, 16.6mmol).

¹HNMR (d₆-DMSO): 6.87 (d, 1H), 7.28 (d, 1H), 7.58-7.71 (m, 2H), 7.98 (t, 1H).

LCMS (5min) Rt = 1.47min. MS m/z 303 [M+H]⁺.

Preparation 11

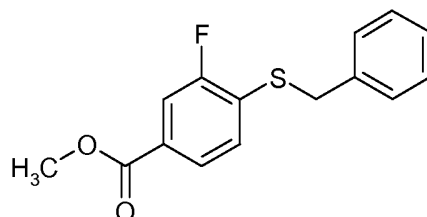
4-(Benzylthio)-3-fluorobenzoic acid



3,4-Difluorobenzoic acid (50g, 320mmol), cesium carbonate (206g, 632mmol) and benzyl mercaptan (37.4mL, 320mmol) were combined in DMSO (500mL) and the reaction mixture heated at 70°C for 3 hours. The reaction mixture was cooled to room temperature and then poured into water (1.5L) before extraction with EtOAc (2 x 750mL). The aqueous was acidified to pH = 1 with 4N HCl (aq) and the precipitate filtered and dried *in vacuo* to provide the title compound as a pale pink coloured solid (84.7g, 320mmol).

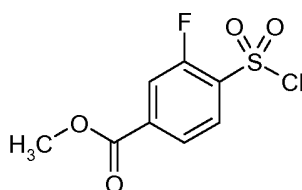
¹HNMR (CDCl₃): 4.2 (s, 2H), 7.3 (m, 6H), 7.75 (m, 2H).

LCMS Rt = 1.55 min. MS m/z 261 [M-H]⁻.

Preparation 12Methyl 4-(benzylthio)-3-fluorobenzoate

A suspension of 4-(benzylthio)-3-fluorobenzoic acid (preparation 11, 81.4g, 0.310mol) in MeOH (800mL) and c.H₂SO₄ (2mL) was heated at reflux for 36 hours. The mixture was cooled to room temperature and the resulting precipitate filtered and washed with hexane. The filtrate was concentrated *in vacuo* and the resulting solid filtered and washed with hexane. The combined solids were dried *in vacuo* to provide title compound as a white solid (60.9g, 0.217mol).

¹HNMR (CDCl₃): 3.90 (s, 3H), 4.18 (s, 2H), 7.22-7.35 (m, 6H), 7.65-7.72 (m, 2H).

Preparation 13Methyl 4-(chlorosulfonyl)-3-fluorobenzoate

To a vigorously stirred solution of methyl 4-(benzylthio)-3-fluorobenzoate (preparation 12, 30.4g, 0.110mol) in DCM (860mL) and 4N HCl (aq) (860mL) at 5°C was added sodium hypochlorite (445mL) dropwise, keeping the temperature below 10°C throughout. Upon complete addition the reaction mixture was allowed to warm to room temperature over 1 hour. Two reactions were carried out on identical scale in parallel (2 x 0.11mol scale) and combined at this point for work-up and purification. The layers were separated and the aqueous extracted with DCM (500mL). The combined organics were washed with a 10%

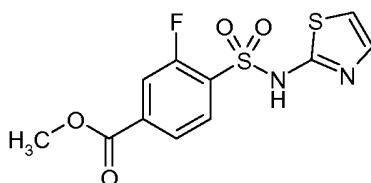
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aqueous solution of sodium metabisulfite (2 x 200mL), brine (200mL), dried (MgSO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel eluting with Hexane/EtOAc (95:5 to 4:1) to provide the title compound as a white solid (53.1g, 0.210mol).

^1H NMR (CDCl_3): 3.99 (s, 3H), 7.95-8.08 (m, 3H).

Preparation 14

Methyl 3-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoate

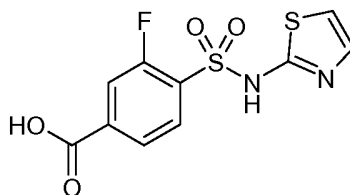


To a solution of 2-aminothiazole (105.2g, 1.05mol) in pyridine (250mL) was added methyl 4-(chlorosulfonyl)-3-fluorobenzoate (preparation 13, 53.1g, 0.21mol) and the mixture stirred at 50°C for 18 hours. The reaction was then allowed to cool to room temperature and added portionwise into 2N HCl (aq) (300mL) and the mixture acidified to pH=1 with 4N HCl (aq). The resulting precipitate was filtered, washed with water and dried *in vacuo* to provide the title compound as a tan coloured solid (31.97g, 0.10mol). This material was used crude for subsequent reactions.

^1H NMR (d_6 -DMSO): 3.88 (s, 3H), 6.88 (d, 1H), 7.29 (d, 1H), 7.77-7.99 (m, 3H).

Preparation 15

3-Fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoic acid



To a suspension of methyl 3-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoate (preparation 14, 32.0g, 0.101mol) in dioxane:water (1:1, 150mL) at 5°C was

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added lithium hydroxide (12.1g, 0.505mol). The mixture was allowed to warm to room temperature and stirred for 4.5 hours. The dioxane was then removed *in vacuo* and the aqueous washed with EtOAc (2 x 100mL). The aqueous was acidified by addition to 2N HCl (aq) (1000mL) and the resulting precipitate filtered and washed with water.

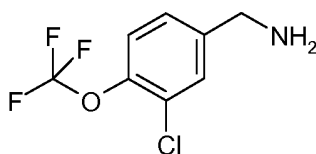
Purification was accomplished *via* recrystallisation from DCM:MeOH (10:1) to provide the title compound as a tan coloured solid (12.9g, 0.043mol).

¹H NMR (d₆-DMSO): 6.88 (d, 1H), 7.29 (d, 1H), 7.72-7.98 (m, 3H).

LCMS (5min) Rt = 1.44min. MS m/z 303 [M+H]⁺

Preparation 16

1-[3-chloro-4-(trifluoromethoxy)phenyl]methanamine



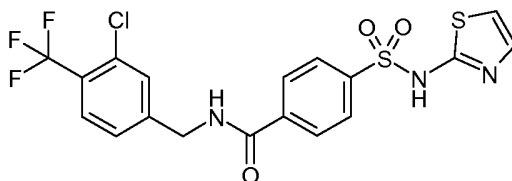
To a solution of 3-chloro-4-(trifluoromethoxy)benzyl bromide (10.0g, 34.5mmol) in DMF (100mL) was added phthalimide (5.6g, 38.0mmol) and potassium carbonate (7.15g, 51.8mmol) and the mixture stirred at 80°C for 5 hours. The mixture was cooled and treated with water (100mL) and the resulting white precipitate filtered, washed with water and dried *in vacuo*. This crude solid (16g) was suspended in methylamine (100mL of a 40% aqueous solution) and water (100mL) and heated in a bomb at 100 °C for 3 hours. Additional methylamine (100mL of a 40% aqueous solution) was added and heating at 100 °C continued for 8 hours. The reaction was then cooled to room temperature and diluted with brine (300mL) and TBME (300mL). The organic layer was separated, dried (Na₂SO₄) then concentrated *in vacuo* to provide the title compound as a yellow oil (9.0g, crude quant.). This material was used crude for subsequent reactions.

¹H NMR (d₆-DMSO): 3.71 (s, 2 H), 7.37-7.41 (m, 1 H), 7.44-7.48 (m, 1 H), 7.63 (d, 1 H)

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Preparation 17

N-[3-chloro-4-(trifluoromethyl)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide



To a suspension of 4-[(1,3-thiazol-2-ylamino)sulfonyl]benzoic acid (preparation 4, 350mg, 1.23mmol) and 1-[3-chloro-4-(trifluoromethyl)phenyl]methanamine (363mg, 1.48mmol) and Et₃N (0.45ml, 3.23mmol) in DMSO (5mL) was added HBTU (560mg, 1.48mmol) and the mixture stirred at room temperature for 18 hours. The reaction was then diluted with EtOAc (10mL) and washed with water (2x10mL) and brine (10mL), dried (Na₂SO₄) then concentrated *in vacuo*. The crude was then triturated with DCM to provide the title compound as a pale orange solid (250mg, 0.53mmol).

¹H NMR (d₆-DMSO): 4.55 (d, 2 H), 6.50 (d, 1 H), 6.95 (d, 1 H), 7.45 (d, 1 H), 7.60 (s, 1 H), 7.75 (d, 1 H), 7.80 (d, 2 H), 7.90 (d, 2 H), 9.20 (t, 1 H)

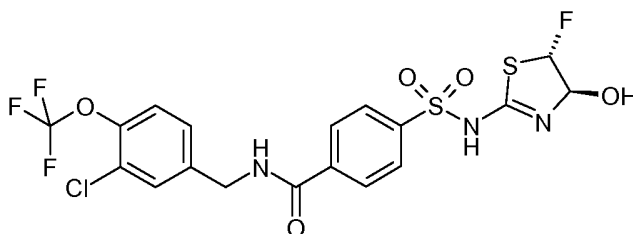
LCMS Rt = 1.42min. MS m/z 476 [M+H]⁺

Structures for preparations 18-21 have been tentatively assigned as the *trans* isomers through comparison with literature methods and data comparison (*J. Chem. Soc., Perkin Trans. 1*, 1978, 1169).

Preparation 18

rac-N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(4R*,5S*)-5-fluoro-4-hydroxy-4,5-dihydro-1,3-thiazol-2-yl]amino)sulfonyl]benzamide

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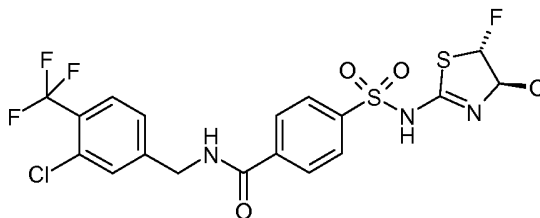
To a solution of N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide (example 2, 605mg, 1.23mmol) in acetonitrile:water (15mL, 1:1) was added SelectFluor® (435mg, 1.23mmol) and the mixture heated to 70°C for 2 hours. Further SelectFluor® (85mg, 0.25mmol) was added and heating continued for 18 hours. The mixture was cooled, diluted with EtOAc (10mL), washed with water (2x10mL) and brine (10mL), dried (Na₂SO₄) and concentrated *in vacuo* before trituration with DCM to provide the title compound an off-white solid (230mg, 0.44mmol).

¹H NMR (d₆-DMSO): 4.50 (d, 2 H), 5.40 (m, 1 H), 6.25-6.40 (d, 1 H), 7.00 (d, 1 H), 7.40 (d, 1 H), 7.55 (d, 1 H), 7.60 (s, 1 H), 7.90 (d, 2 H), 8.05 (d, 2 H), 9.25 (t, 1 H), 10.40 (s, 1 H)

LCMS Rt = 1.47min. MS m/z 528 [M+H]⁺

Preparation 19

rac-N-[3-chloro-4-(trifluoromethyl)benzyl]-4-({[(4R*,5S*)-5-fluoro-4-hydroxy-4,5-dihydro-1,3-thiazol-2-yl]amino}sulfonyl)benzamide



Prepared according to preparation 18 using N-[3-chloro-4-(trifluoromethyl)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide (preparation 17, 250mg, 0.53mmol) to provide the title compound as a pale yellow solid (170mg, 0.33mmol).

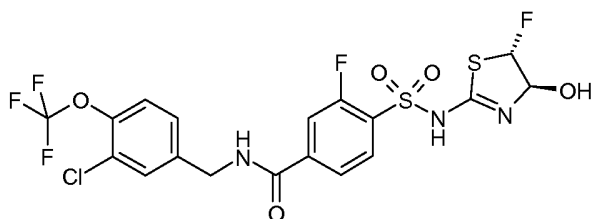
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^1H NMR (d_6 -DMSO): 4.55 (d, 2 H), 5.40 (m, 1 H), 6.25-6.40 (d, 1 H), 7.00 (d, 1 H), 7.45 (d, 1 H), 7.65 (s, 1 H), 7.80 (d, 1 H), 7.90 (d, 2 H), 8.05 (d, 2 H), 9.30 (t, 1 H), 10.40 (s, 1 H)

LCMS Rt = 1.45min. MS m/z 510 $[\text{M}+\text{H}]^+$

Preparation 20

rac-N-[3-chloro-4-(trifluoromethoxy)benzyl]-3-fluoro-4-({[(4R*,5S*)-5-fluoro-4-hydroxy-4,5-dihydro-1,3-thiazol-2-yl]amino}sulfonyl)benzamide



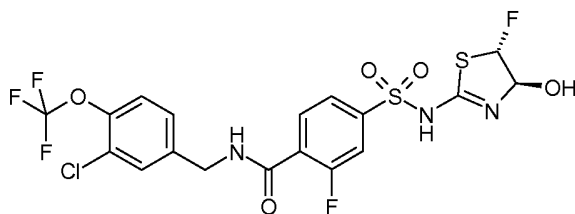
Prepared according to preparation 18 using N-[3-chloro-4-(trifluoromethoxy)benzyl]-3-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide (example 1, 430mg, 0.84mmol) to provide the title compound as a white solid (410mg, 0.75mmol).

^1H NMR (d_6 -DMSO): 4.50 (d, 2 H), 5.40 (m, 1 H), 6.25-6.40 (d, 1 H), 7.00 (d, 1 H), 7.40 (d, 1 H), 7.55 (d, 1 H), 7.60 (s, 1 H), 7.80-7.85 (m, 2 H), 7.90 (t, 1 H), 9.30 (t, 1 H), 10.50 (s, 1 H)

LCMS Rt = 1.54min. MS m/z 546 $[\text{M}+\text{H}]^+$

Preparation 21

rac-N-[3-chloro-4-(trifluoromethoxy)benzyl]-2-fluoro-4-({[(4R*,5S*)-5-fluoro-4-hydroxy-4,5-dihydro-1,3-thiazol-2-yl]amino}sulfonyl)benzamide



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Prepared according to preparation 18 using N-[3-chloro-4-(trifluoromethoxy)benzyl]-2-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide (example 3, 290mg, 0.57mmol) to provide the title compound as a white solid (165mg, 0.30mmol).

¹H NMR (d₆-DMSO): 4.50 (d, 2 H), 5.40 (m, 1 H), 6.25-6.40 (d, 1 H), 7.00 (d, 1 H), 7.40 (d, 1 H), 7.55 (d, 1 H), 7.60-7.70 (m, 3 H), 7.80 (t, 1 H), 9.10 (t, 1 H), 10.50 (s, 1 H)

LCMS Rt = 1.55min. MS m/z 546 [M+H]⁺

The ability of the compounds of the invention to block the Nav1.3 (or SCN3A) channel, or the Nav 1.5 (or SCN5A) channel, were measured using the assay described below.

Cell line construction and maintenance

Human Embryonic Kidney (HEK) cells were transfected with an hSCN3A construct using lipofectamine reagent (Invitrogen), using standard techniques. Cells stably expressing the hSCN3A constructs were identified by their resistance to G-418 (400 µg/ml). Clones were screened for expression using the whole-cell voltage-clamp technique.

Cell Culture

HEK cells stably transfected with hSCN3A were maintained in DMEM medium supplemented with 10% heat-inactivated fetal bovine serum and 400 µg/ml G418 sulfate in an incubator at 37°C with a humidified atmosphere of 10% CO₂. For HTS, cells were harvested from flasks by trypsinization and replated in an appropriate multi-well plate (typically 96 or 384 wells/plate) such that confluence would be achieved within 24 hours of plating. For electrophysiological studies, cells were removed from the culture flask by brief trypsinization and replated at low density onto glass cover slips. Cells were typically used for electrophysiological experiments within 24 to 72 h after plating.

Electrophysiological Recording

Cover slips containing HEK cells expressing hSCN3A were placed in a bath on the stage of an inverted microscope and perfused (approximately 1 ml/min) with extracellular solution of the following composition: 138 mM NaCl, 2 mM CaCl_2 , 5.4 mM KCl, 1 mM MgCl_2 , 10 mM glucose, and 10 mM HEPES, pH 7.4, with NaOH. Pipettes were filled with an intracellular solution of the following composition: 135 mM CsF, 5 mM CsCl, 2 mM MgCl_2 , 10 mM EGTA, 10 mM HEPES, pH 7.3 to 7.4, and had a resistance of 1 to 2 mega ohms. The osmolarity of the extracellular and intracellular solutions was 300 mmol/kg and 295 mmol/kg, respectively. All recordings were made at room temperature (22-24°C) using AXOPATCH 200B amplifiers and PCLAMP software (Axon Instruments, Burlingame, CA) or PatchXpress 7000 hardware and associated software (Axon Instruments, Burlingame, CA).

hSCN3A currents in HEK cells were measured using the whole-cell configuration of the patch-clamp technique (Hamill et al., 1981). Uncompensated series resistance was typically 2 to 5 mega ohms and >85% series resistance compensation (50% for PatchXpress) was routinely achieved. As a result, voltage errors were negligible and no correction was applied. Current records were acquired at 20 to 50 KHz and filtered at 5 to 10 KHz.

HEK cells stably transfected with hSCN3A were viewed under Hoffman contrast optics and placed in front of an array of flow pipes emitting either control or compound-containing extracellular solutions. All compounds were dissolved in dimethyl sulfoxide to make 10 mM stock solutions, which were then diluted into extracellular solution to attain the final concentrations desired. The final concentration of dimethyl sulfoxide (<0.3% dimethyl sulfoxide) was found to have no significant effect on hSCN3A sodium currents.

The voltage-dependence of inactivation was determined by applying a series of depolarizing prepulses (8 sec long in 10 mV increments) from a negative holding potential. The voltage was then immediately stepped to 0 mV to assess the

magnitude of the sodium current. Currents elicited at 0 mV were plotted as a function of prepulse potential to allow estimation of the voltage midpoint of inactivation ($V_{1/2}$). Cells were then voltage clamped at the empirically determined $V_{1/2}$.

Compounds were tested for their ability to inhibit hSCN3A sodium channels by activating the channel with a 20 msec voltage step to 0 mV following an 8 second conditioning prepulse to the empirically determined $V_{1/2}$. Compound effect (% inhibition) was determined by difference in current amplitude before and after application of test compounds. For ease of comparison, "estimated IC-50" (EIC-50) values were calculated from single point electrophysiology data by the following equation, (tested concentration, μ M) X (100-% inhibition/% inhibition). Inhibition values <20% and >80% were excluded from the calculation.

In some cases electrophysiological assays were conducted with PatchXpress 7000 hardware and associated software (Molecular Devices Corp). All assay buffers and solutions were identical to those used in conventional whole-cell voltage clamp experiments described above. hSCN3A cells were grown as above to 50% – 80% confluency and harvested by trypsinization. Trypsinized cells were washed and resuspended in extracellular buffer at a concentration of 1×10^6 cells/ml. The onboard liquid handling facility of the PatchXpress was used for dispensing cells and application of test compounds. Determination of the voltage midpoint of inactivation was as described for conventional whole-cell recordings. Cells were then voltage-clamped to the empirically determined $V_{1/2}$ and current was activated by a 20 msec voltage step to 0 mV.

Electrophysiological assays were also conducted using the Ionworks Quattro automated electrophysiological platform (Molecular Devices Corp). Intracellular and extracellular solutions were as described above with the following changes, 100 μ g/ml amphotericin was added to the intracellular solution to perforate the membrane and allow electrical access to the cells. hSCN3A cells were grown and harvested as for PatchXpress and cells were resuspended in extracellular

solution at a concentration of $3\text{--}4 \times 10^6$ cells/ml. The onboard liquid handling facility of the Ionworks Quattro was used for dispensing cells and application of test compounds. A voltage protocol was then applied that comprised of a voltage step to fully inactivate the sodium channels, followed by a brief hyperpolarized recovery period to allow partial recovery from inactivation for unblocked sodium channels, followed by a test depolarized voltage step to assess magnitude of inhibition by test compound. Compound effect was determined based on current amplitude difference between the pre-compound addition and post-compound addition scans.

High-Throughput Screening Assays

Confluent cells in multi-well plates were incubated with a permeant radioactive ion (^{22}Na , ^{14}C -guanidinium, etc) for 4-16 hours to allow uptake of the radiotracer. Excess radioactive ions were removed by washing with prewarmed buffer of the following composition: 138 mM NaCl, 2 mM CaCl_2 , 5.4 mM KCl, 1 mM MgCl_2 , 10 mM glucose, and 10 mM HEPES, pH 7.4, with NaOH. Efflux was initiated by addition of buffer containing any necessary chemical activators (e.g., 100 μM veratridine, 10 – 20 $\mu\text{g/ml}$ Lqh scorpion venom, etc.). Various concentrations of test compounds or reference sodium channel blockers were added concurrently with the initiation of efflux. Efflux was allowed to progress for a defined period of time, typically 30 – 90 minutes, at 37°C in a humidified 10% CO_2 atmosphere. Stimulated efflux was determined by collecting the extracellular solution and transferring to a multiwell plate for scintillation counting. Residual intracellular radioactivity was also determined by scintillation counting following lysis of the cells in the assay plate. Inhibition of efflux was determined by comparing efflux in the presence of test compounds to efflux in untreated control cells.

SCN5A Assay

The SCN5A assay is performed in HEK cells transfected with Human SCN5A in the same way as described for the SCN3A assay.

Exemplified compounds have been tested in the SCN3A and SCN5A assays described above and the results are shown below.

	SCN3A EIC50 (μM)	SCN5A EIC50 (μM)	Ratio SCN3A/SCN5A
Example 1	0.015	15.20	1020
Example 2	0.028	3.82	137
Example 3	0.088	2.09	24
Example 4	0.066	13.16	199
Example 5	0.026	3.61	138
Example 6	0.012	1.97	164
Example 7	0.019	1.55	80
Example 8	0.009	3.82	439

Example 10 was also tested in the in vitro screen described above. It exhibited no inhibition of SCN3A at a concentration of 1 μM.

Certain compounds or formulations of the invention were also tested in vivo using the protocol described below. All experiments were conducted under protocols which had previously been approved by Icagen's Institutional Animal Care and Use Committee (IACUC).

Animals

Double-cannula (jugular vein and femoral vein) male Sprague-Dawley rats were obtained from Charles River Laboratories (Raleigh, NC). The exception to this was for the SDD formulation experiment where single cannula rats (jugular vein) were utilized (Charles River Laboratories, Raleigh, NC). Prior to the experiment, the rats were individually housed and given ad libitum access to food and water in a climate-controlled vivarium and then, for all experiments except those involving the SDD formulation for Example 11, were fasted for 24 hr prior to the start of the experiment. On the day of the experiment the mean ± S.E.M. body weight was 218 ± 2.8 g. Test formulations were prepared by forming a suspension of either the compounds or formulations of the invention in a vehicle

of either 0.5% methylcellulose or 0.5% methylcellulose/0.1% Tween80 as indicated in the table Z below. The test formulation was administered via oral gavage and blood was sampled from either the femoral vein cannula, or, for the test formulations comprising the SDD formulation of Example 11, from a jugular vein cannula. During all experiments the animals had ad libitum access to water. For those experiments where the animals had been fasted, food was replaced after 4 hr on the day of the experiment.

Sample collection and analysis

First approximately 0.2 mL of blood was sampled into a 3 mL syringe attached to the catheter. Next, the 3 mL syringe was removed and replaced with a clean 1 mL syringe and approximately 0.25 mL of blood was removed. The 1 mL syringe with the blood sample was then removed and a 3 mL syringe containing EDTA/saline was used to flush the cannula (approximately 0.3 mL). The blood sample in the 1 mL syringe was gently pushed into a pre-labeled microtainer blood tube (EDTA) and placed on a test tube rocker. The blood was allowed to rock for at least 10 min but for no longer than 60 min. Next, microtainers were placed in a refrigerated centrifuge and spun at 4200 RPM for 20 min. Samples were then plated into a 96-well plate. For experiments having a 24-hr time point, the 96-well plate was placed in a freezer overnight and then removed when the 24-hr sample was ready to plate. The well plate was then transferred on dry ice to the analytical laboratory with a corresponding plate map that contained the relevant information (e.g., animal number, dose, time point, etc...).

Bioanalytical methods

Unless otherwise specified samples were quantified using Turbulent Flow Chromatography (TFC)-MS/MS. Compounds were analyzed using a Thermo TSQ Quantum Vantage triple quadrupole mass spectrometer (HESI-II, 250C, sheath gas =50, ThermoFisher Scientific, San Jose, CA). Plasma samples diluted 1:10 with water containing internal standard were injected (10 µL) using a

CTC Analytics HTS Pal autosampler (CTC Analytics, Zwingen, Switzerland) onto a 0.5 X 50 mm Cyclone-P HTLC column of the Transcend TLX2 TFC system (Cohesive Technologies, Franklin, MA; binary LC pumps from Agilent Technologies, Santa Clara, CA) for on-line extraction with buffer A at 1.5 mL/min, followed by elution onto a 50 X 2.0 mm Synergy Hydro-RP 4 μ (Phenomenex, Torrance, CA) analytical column. Samples were eluted off the analytical column to the mass spectrometer with a gradient from 100 % buffer A (water:4mM ammonium formate:1% formic acid) to 100% methanol in 1 minute at 600 μ L/min. MS/MS mrm product ions and conditions used had been optimized for each compound previous to start of the analyses.

Samples of the spray dried dispersion test compound (Example 11) were quantified as set out below. 25 μ L aliquots of a standard (STDs), quality controls (QCs) and test compound samples were aliquoted into a 96 well block along with 200 μ L of acid buffer pH4 containing internal standard. Samples were extracted using 1000 μ L of TBME (tert-butyl methyl ether) and thoroughly mixed by automation (Hamilton robotics). After centrifugation at 3000 rpm for 5 min, the organic layer was transferred into a clean 96 well block and evaporated to dryness in a Turbovap[®] at 40°C under a stream of nitrogen. The residue was reconstituted in 200 μ L of with Mobile Phase A (A: 2mM NH₄OAc in 90:10 (v/v) H₂O:MeOH, 0.027% formic acid). Samples were analysed using Applied Biosystems/MDS Sciex API 4000. Analyte separation onto a Chromolith Speed Rod RP C18, 50 x 4.6mm, 5 μ m column using Agilent 1100 LC pumps (Agilent Technologies) at a gradient flow rate 1.2 mL/min with Mobile Phase A (A: 2mM NH₄OAc in 90:10 (v/v) H₂O:MeOH, 0.027% formic acid) and Mobile Phase B (2mM NH₄OAc in 10:90 (v/v) H₂O:MeOH, 0.027% formic acid). MS/MS mrm product ions and conditions used had been optimized for each compound prior to start of the analyses.

Results

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A pharmacokinetic analysis was carried out comparing neutral Example 2 with its corresponding potassium salt, prodrug (Example 10), and its sprayed dried dispersion (SDD) (Example 11) at two dose levels. Example 2, its corresponding potassium salt and the prodrug (Example 10) were all dosed at 100 mg/kg with plasma sampling over 24 hours. The SDD (Example 11) was dosed at 30 and 100 mg/kg active and plasma samples were taken out to 4 hours.

Table Z

Compound	Form	Vehicle	Dose (mg/kg)	Dose volume (mL/kg)
Example 2	Neutral	0.5% methylcellulose	100	4
Example 2 potassium salt	Potassium salt	0.5% methylcellulose	100	4
Example 10	Prodrug	0.5% methylcellulose	100	2
Example 11	SDD formulation	0.5% MethylCellulose: 0.1%Tween 80	30	4
Example 11	SDD formulation	0.5% MethylCellulose: 0.1%Tween 80	100	4

The results are shown in Figure 1. Figure 1 shows that the potassium salt of Example 2, prodrug (Example 10) and SDD formulation (Example 11), when dosed at 100 mg/kg, all provide substantially greater exposure than the neutral compound Example 2 as demonstrated by the significantly improved C_{max} results. Furthermore, as shown in Figure 2, the potassium salt of Example 2 and the prodrug (Example 10) both demonstrated an approximately 30-fold greater

AUC when compared to the neutral compound (Example 2), again supporting the improved exposure of these alternative forms. Finally the 100 mg/kg SDD had a C_{\max} of approximately 120-fold over neutral Example 2 and the 30 mg/kg SDD demonstrated an approximately 10-fold improvement.

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CLAIMS

1. A compound selected from the group consisting of:

N-[3-chloro-4-(trifluoromethoxy)benzyl]-3-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide;

N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide;

N-[3-chloro-4-(trifluoromethoxy)benzyl]-2-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide;

N-[3-chloro-4-(trifluoromethyl)benzyl]-2-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide;

N-[3-chloro-4-(trifluoromethoxy)benzyl]-2-fluoro-4-[(5-fluoro-1,3-thiazol-2-yl)amino]sulfonyl}benzamide;

N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(5-fluoro-1,3-thiazol-2-yl)amino]sulfonyl}benzamide;

N-[3-chloro-4-(trifluoromethyl)benzyl]-4-[(5-fluoro-1,3-thiazol-2-yl)amino]sulfonyl}benzamide; and

N-[3-chloro-4-(trifluoromethoxy)benzyl]-3-fluoro-4-[(5-fluoro-1,3-thiazol-2-yl)amino]sulfonyl}benzamide;

and the pharmaceutically acceptable salts, solvates and tautomers thereof.

2. A compound according to Claim 1, selected from the group consisting of:

N-[3-chloro-4-(trifluoromethoxy)benzyl]-3-fluoro-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide

N-[3-chloro-4-(trifluoromethoxy)benzyl]-4-[(1,3-thiazol-2-ylamino)sulfonyl]benzamide

and the pharmaceutically acceptable salts, solvates and tautomers thereof.

3. A pharmaceutical composition comprising a compound according to Claim 1 or 2, or a pharmaceutically acceptable salt, solvate or tautomer thereof, together with a pharmaceutically acceptable excipient.
4. A compound according to Claim 1 or 2, or a pharmaceutically acceptable salt, solvate or tautomer thereof, for use as a medicament.
5. The use of a compound according to Claim 1 or 2, or a pharmaceutically acceptable salt, solvate, tautomer or composition thereof, for the manufacture of a medicament to treat a disease or condition for which a Nav1.3 channel modulator is indicated.
6. The use as claimed in Claim 5 wherein the disease or condition is pain.
7. A method of treating a disease or condition for which a Nav1.3 channel modulator is indicated in a mammal, including administering to said mammal an effective amount of a compound according to Claim 1 or 2, or a pharmaceutically acceptable salt, solvate, tautomer or composition thereof.
8. A method as claimed in claim 7, wherein the mammal is a human being.
9. A method as claimed in claim 7 or claim 8, wherein the disease or condition is pain.
10. A compound according to Claim 1 or 2, or a pharmaceutically acceptable salt, solvate or tautomer thereof, for use in the treatment of a disease or condition for which a Nav1.3 channel modulator is indicated.
11. A compound according to Claim 1 or 2, or a pharmaceutically acceptable salt, solvate or tautomer thereof, for use in the treatment of pain.

12. A combination of a compound according to Claim 1 or 2, or a pharmaceutically acceptable salt, solvate or tautomer thereof, and another pharmacologically active agent.

Figure 1- PK data (log-linear)

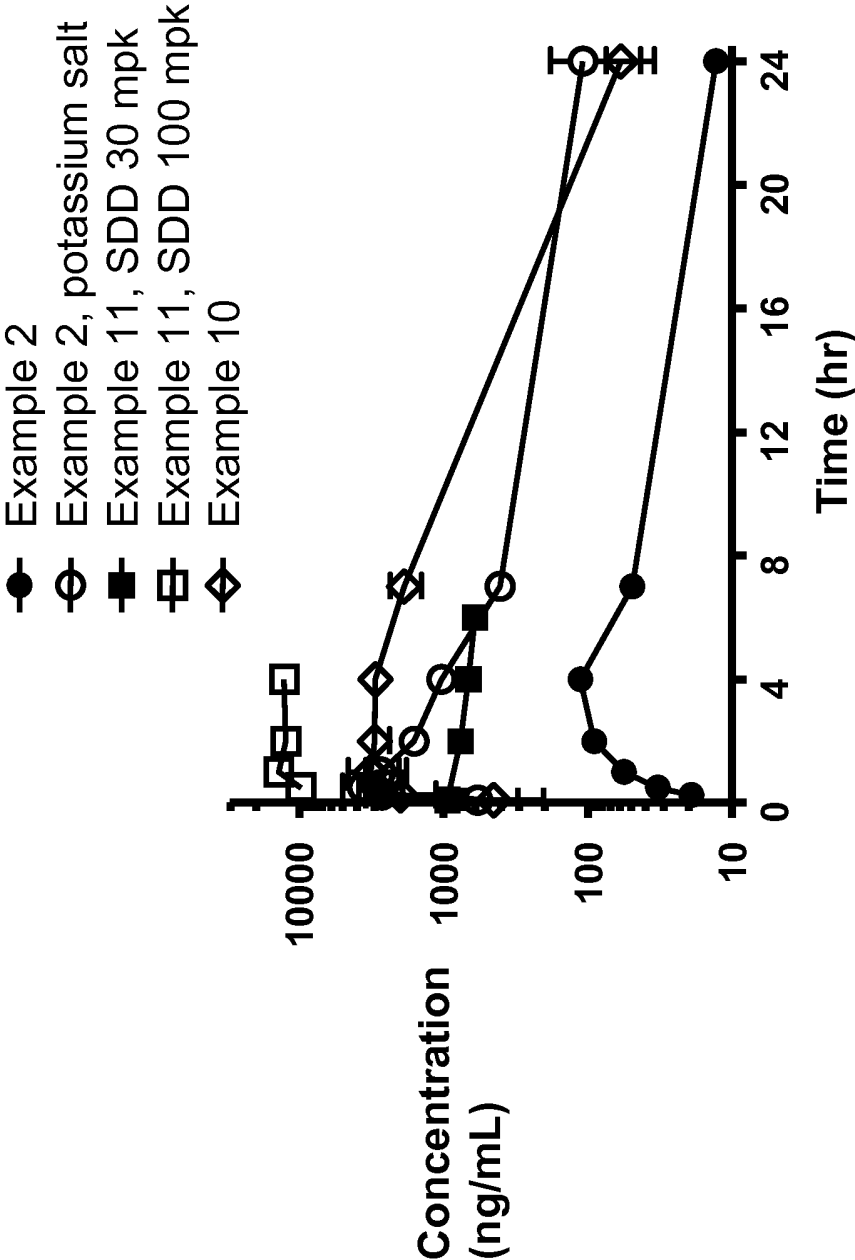
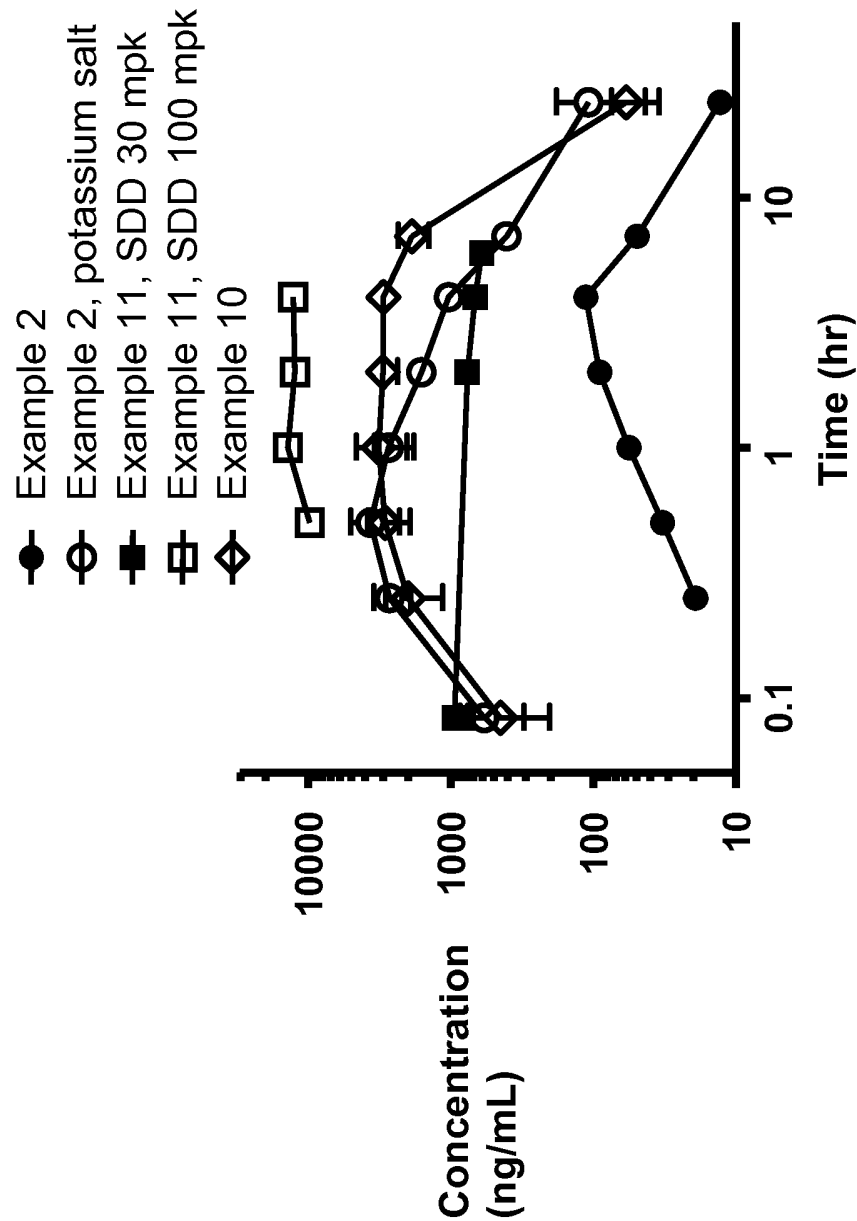


Figure 2 PK data (log-log)



INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2009/053971

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D277/52 A61K31/4168 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation, to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/013914 A (VERTEX PHARMA [US]; GONZALES JESUS E III [US]; TERMIN ANDREAS P [US];) 17 February 2005 (2005-02-17) cited in the application See claim 1 & examples.	1-12
P,X	WO 2008/118758 A (ICAGEN INC [US]; PFIZER LTD [GB]; MARRON BRIAN EDWARD [US]; FRITCH PAU) 2 October 2008 (2008-10-02) cited in the application the whole document	1-12

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2009/053971

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005013914 A	17-02-2005	AU 2004263179 A1 CA 2539227 A1 EP 1673357 A2 KR 20060073930 A	17-02-2005 17-02-2005 28-06-2006 29-06-2006
WO 2008118758 A	02-10-2008	AR 065824 A1 CL 8352008 A1 EP 1995241 A1 PA 8773501 A1 US 2009143358 A1 UY 30978 A1	01-07-2009 03-10-2008 26-11-2008 23-04-2009 04-06-2009 31-10-2008